[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

The Acid-catalyzed Anomerization of the D-Glucose Pentaacetates. A Kinetic Thermodynamic and Mechanistic Study[1]

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β-D-Glucose pentaacetate and its anomer in acetic anhydride containing sulfuric acid have been found to anomerize to an equilibrium mixture in accordance with a first order rate expression. The rate of anomerization proved directly proportional to the concentration of sulfuric acid catalyst, and independent of the concentrations of glucose pentaacetate or acetic anhydride. The rate of anomerization was not retarded by addition of lithium bisulfate. Acetic acid and ethers, substances basic to sulfuric acid, repressed the rate of anomerization. A quantitative theory explaining this retarding effect has been developed. The anomerization process has been shown to be an inversion specific for the acetoxy grouping at the anomeric center. The equilibrium position of the anomerization and the rate of anomerization have been studied as a function of temperature in a 50:50 mixture of acetic anhydride and acetic acid. The standard heat, entropy and free energy of anomerization in this solvent mixture have been calculated. Standard heats, entropies and free energies of activation for the forward and reverse reactions have also been computed. A mechanism for the anomerization process has been proposed. The mechanism constitutes a sufficient, though perhaps not a necessary theory to rationalize all the known kinetic and chemical facts regarding the particular anomerizing system studied. 1-Propionyl-2,3,4,6-tetraacetyl-α-D-glucose and its anomer have been described for the first time. A convenient synthesis of pentaacetyl-1-thio-β-D-glucose has been described, and the structure of this substance established by reductive desulfurization.

Introduction

The anomerizing action of Lewis acids on acetylated sugars is well known and has found frequent application to preparing members of the α-series of these compounds. Thus, anhydrous zinc chloride in a mixture of acetic anhydride and acetic acid has been used by Hudson and co-workers to convert the β-acetates of xylose,[2] mannose,[3] galactose[4] and lactose[5] into the α-anomers, while Cramer and Pacsu[6] employed this catalyst to convert α-D-fructose pentaacetate into the β-form. Stannic chloride has been used by Pacsu[7] to change β-D-glucose and β-D-mannose pentaacetates into the α-anomers in 80% yield, while sulfuric acid was found to anomerize β-D-glucose pentaacetate[8] and β-D-mannoheptose hexaacetate.[9] Wolfrom[10] has noted a variant of this reaction, wherein the β-acetates of mannose, galactose, and lactose were anomerized by the action of dry sodium hydroxide in dioxane. It is noteworthy that Georg[11] was unable to convert α-D-glucose pentaacetate into the β-anomer with sodium acetate in acetic anhydride.

Several authors have pointed out the equilibrium nature of anomerization. In 1905 Jungius[12] reported that either α- or β-D-glucose pentaacetate was convertible by zinc chloride to an equilibrium mixture having the composition α:β/9:1. Freudenberg and Soff[8] found α:β/88:12 when sulfuric acid catalyzed the anomerization of either pentaacetate. Using the integrated polarimetric rate expression (1)

$$k_1 + k_2 = \frac{2.303}{t} \log \frac{r_0 - r_e}{r_t - r_e} \qquad (1)$$

$$\alpha \underset{k_2}{\overset{k_1}{\rightleftarrows}} \beta \qquad (2)$$

of Hudson[13] for the simple equilibrium (2), Jungius found the isomerization first order, with $k_1 + k_2$ for the D-glucose pentaacetates having the value 0.0097 min.$^{-1}$ (average) at 35° and 0.030 min.$^{-1}$ at 45° in a 2% solution of zinc chloride in acetic anhydride.

We have been interested in studying in greater detail the kinetics of anomerization of the D-glucose pentaacetates in order to elucidate its mechanism. Sulfuric acid, rather than a metal halide, has been the catalyst of choice due to ease of handling.

Effect of Catalyst Concentration

When a solution 0.1 M in β-D-glucose pentaacetate and 0.5 M in sulfuric acid in a 50:50 mixture of acetic anhydride and acetic acid was placed at 25° in a polarimeter tube, rapid mutarotation resulted. The values of $k_1 + k_2$, calculated at each point by means of Equation (1), are given in Table I. The mean value is 0.0326 ± 0.0004 min.$^{-1}$. α-D-Glucose pentaacetate under identical conditions gave $k_1 + k_2$ as 0.0338 ± 0.0005 min.$^{-1}$. These results accord with those of Jungius[12] using zinc chloride.

TABLE I

MUTAROTATION OF β-D-GLUCOSE PENTAACETATE AT 25° IN 50:50 Ac_2O–AcOH IN THE PRESENCE OF 0.5 M H_2SO_4

Time, min.	Observed rotation, °	$k_1 + k_2$, min.$^{-1}$
5	1.56	0.0328
10	2.50	.0329
15	3.28	.0330
20	3.93	.0328
25	4.49	.0327
30	4.97	.0330
40	5.70	.0326
50	6.23	.0324
60	6.62	.0324
75	7.01	.0335
215	7.65	

Keeping other factors constant and varying only the concentration of sulfuric acid, these experiments were repeated to determine the effect of the catalyst concentration on the rate. The quantitative relationship between catalyst concentration and $k_1 + k_2$ is shown in Table II and Fig. 1. The variation is very nearly linear. Equation (1) may be modified empirically to (3) to take into account the

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(1) Presented before the Division of Sugar Chemistry, 118th Meeting of the American Chemical Society, Chicago, September, 1950.

(2) Hudson and Johnson, THIS JOURNAL, **37**, 2748 (1915).

(3) Hudson and Dale, *ibid.*, **37**, 1280 (1915).

(4) Hudson and Parker, *ibid.*, **37**, 1589 (1915).

(5) Hudson and Johnson, *ibid.*, **37**, 1270 (1915).

(6) Cramer and Pacsu, *ibid.*, **59**, 711 (1937).

(7) Pacsu, *Ber.*, **61**, 137 (1928).

(8) Freudenberg and Soff, *ibid.*, **69**, 1245 (1936).

(9) Montgomery and Hudson, THIS JOURNAL, **56**, 2463 (1934).

(10) Wolfrom, *ibid.*, **59**, 364 (1937).

(11) Georg, *Helv. Chim. Acta*, **12**, 261 (1929).

(12) Jungius, *Z. physik. Chem.*, **52**, 101 (1905).

(13) Hudson, *ibid.*, **44**, 487 (1903).

TABLE II

VARIATION OF $k_1 + k_2$ FOR D-GLUCOSE PENTAACETATES WITH CATALYST CONCENTRATION AT 25° IN 50:50 Ac_2O–AcOH

D-Glucose pentaacetate	H_2SO_4 (mole/liter)	$k_1 + k_2$ (min.$^{-1}$)	$\frac{k_1 + k_2}{[H_2SO_4]}$ (liter/mole-min.)
β	1.00	0.0764 ± 0.00120	0.0764
β	0.50	.0326 ± .00040	.0652
α	.50	.0338 ± .00050	.0676
β	.40	.0275 ± .00014	.0688
β	.30	.0196 ± .00011	.0654
α	.30	.0185 ± .00130	.0617
β	.20	.0122 ± .00010	.0610
β	.10	.00578 ± .00007	.0578
β	.05	.00282 ± .00007	.0565
α	.05	.00297 ± .00035	.0595

effect of the catalyst concentration. The fair validity of (3)

$$k_1 + k_2 = \frac{1}{[H_2SO_4]} + \frac{2.303}{t} \times \log \frac{r_0 - r_e}{r_t - r_e} \quad (3)$$

is seen in Table II, where the mean value of the quotient is 0.0640.

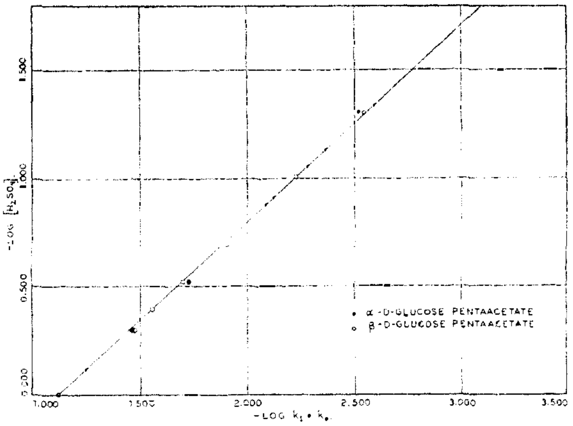


Fig. 1.—Variation in rate of anomerization of D-glucose pentaacetates with acid concentration in 50–50 Ac_2O–AcOH.

As discussed later, anomerization occurred more rapidly in pure acetic anhydride than in mixtures containing acetic acid. In pure acetic anhydride, also, the approximate linearity between rate and acid concentration was found to hold, as seen in Table III. The average deviations from the mean values of $k_1 + k_2$ in Table III are greater than the corresponding values in Table II. This is due to the greater rates of reaction in Table III, and the accompanying difficulty in following the reactions accurately in a polarimeter. The half-life of the first reaction in Table III, for example, is only about 1.2 minutes.

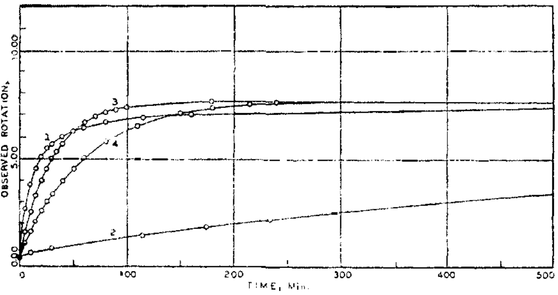
TABLE III

VARIATION OF $k_1 + k_2$ FOR β-D-GLUCOSE PENTAACETATE WITH CATALYST CONCENTRATION AT 25° IN ACETIC ANHYDRIDE

$[H_2SO_4]$ (mole/liter)	$k_1 + k_2$ (min.$^{-1}$)	$\frac{k_1 + k_2}{[H_2SO_4]}$ (liters/mole-min.)
0.50	0.572 ± 0.017	1.144
.40	.479 ± .018	1.196
.30	.317 ± .021	1.056
.20	.205 ± .015	1.025

Catalyst Aging

Attempting to secure more accurate results in the rate experiments, we prepared stock 1.0 *M* sulfuric acid in 50:50 acetic anhydride–acetic acid, and used aliquots of this in preparing reaction mixtures of known catalyst concentration. When done, however, it was found that the $k_1 + k_2$ values depended upon how long the stock solution had stood before use. The same phenomenon was noticed with pure acetic anhydride, deterioration of the catalyst solution here being more rapid. Figure 2 illustrates this "aging" process, wherein the ability of the catalyst solution to cause anomerization decreases with time. "Aging" was also directly evident in some of the mutarotations, especially in solutions containing high concentrations of acetic anhydride. Here the phenomenon appeared as a gradual, monotonic decrease in $k_1 + k_2$ as the reaction proceeded. Table IV shows a particularly marked instance of the "aging" process giving progressively decreasing rate values.



Curve	$[H_2SO_4]$ *M*	Solvent % Ac_2O	Solvent % AcOH	Age, days	$k_1 + k_2$, min.$^{-1}$
1	0.10	100	0	0	0.0535
2	.10	100	0	1	~ .0015
3	.50	50	50	1	.0333
4	.50	50	50	16	.0163

Fig. 2.—Effect of age of catalyst solution on mutarotation of β-D-glucose pentaacetate.

The occurrence of "aging" required preparing fresh catalyst solution for each run and, in cases where its effect was apparent in the rate values, necessitated the rather arbitrary selection of values included in the averages. In such cases, only the early rate values were included. It is probable that "aging" was one of our major sources of experimental error, especially in experiments using high concentrations of acetic anhydride in the solvent.

TABLE IV

MUTAROTATION OF β-D-GLUCOSE PENTAACETATE IN ACETIC ANHYDRIDE CONTAINING 0.2 *M* SULFURIC ACID AT 25°

Time, min.	Observed rotation, °	$k_1 + k_2$, min.$^{-1}$
2	3.19	0.235
4	4.64	.216
6	5.53	.202
8	6.12	.192
10	6.51	.182
15	7.05	.163
25	7.44	.138
40	7.62	.124

The cause of "aging" has not been determined but seems probably some irreversible reaction of the catalyst with acetic anhydride. The formation of mixed anhydrides between acetic and sulfuric acids is one plausible explanation. In any case, the concentration of sulfuric acid is continuously diminished by the occurrence of the reaction. Since the rate of anomerization is directly proportional to the catalyst concentration, $k_1 + k_2$ decreases progressively as the solution stands. In this connection, it is significant that solutions of sulfuric acid in acetic anhydride darkened on prolonged standing.

Absence of Salt Effect

To see if the rate of anomerization was affected by the presence of inert salt, the experiment in Table I was duplicated in an identical solution 1.0 *M* in lithium bisulfate. Here $k_1 + k_2$ was 0.0286 min.$^{-1}$, agreeing approximately within experimental error with the value 0.0326 min.$^{-1}$ obtained before. While these results suggest the absence of salt effect, they might also be interpreted as follows. The ionization of sulfuric acid in acetic anhydride (Equation (4)) might be repressed by addition of bisul-

$$H_2SO_4 + Ac_2O \longrightarrow Ac_2OH^+ + HSO_4^- \quad (4)$$
$$H_2SO_4 + AcOH \longrightarrow AcOH_2^+ + HSO_4^- \quad (5)$$

fate, causing a decrease in rate (it will be shown later that $[Ac_2OH^+]$ actually determines the rate), while the salt effect due to lithium bisulfate might increase the rate. If these opposing factors fortuitously balanced, the rate would appear unchanged. To test this possibility, two mutarotations were conducted with still different quantities of catalyst and salt. Again (Table V) identical rates were obtained.

TABLE V

TEST FOR SALT EFFECT IN ANOMERIZATION OF β-D-GLUCOSE PENTAACETATE IN 50:50 Ac_2O–AcOH AT 25°

$[H_2SO_4]$, mole/liter	$[LiHSO_4]$, mole/liter	$k_1 + k_2$, min.$^{-1}$
0.50	0.00	0.0326 ± 0.0004
.50	1.00	.0287 ± .0007
.30	0.00	.0196 ± .0001
.30	0.10	.0200 ± .0001

The similarity of rates in each set of experiments indicates that anomerization is not affected appreciably by the presence of added salt. Furthermore, since excess lithium bisulfate did not retard the anomerization, it is indicated that sulfuric acid ionizes completely in mixtures of acetic anhydride and acetic acid according to equations (4) and (5). It is interesting that 0.5 *M* lithium bisulfate in the absence of acid catalyzed the anomerization of β-D-glucose pentaacetate in the same solvent only at an extremely slow rate ($k_1 + k_2$ *ca.* 0.0005 min.$^{-1}$). This suggests that ionization of bisulfate to form sulfate and the conjugate acids Ac_2OH^+ and $AcOH_2^+$ occurs only to a very limited extent compared to the primary ionization of sulfuric acid in such mixtures.

Effect of Glucose Pentaacetate Concentration

The effect of β-D-glucose pentaacetate concentration on the rate of anomerization was next investigated under various conditions. As seen in Table VI the rates in each series were identical approximately within experimental error. Unfortunately, solubility limitations on the one hand and polarimeter reading limitations on the other, prevented extending the concentration range of β-D-glucose pentaacetate much beyond a factor of four.

TABLE VI

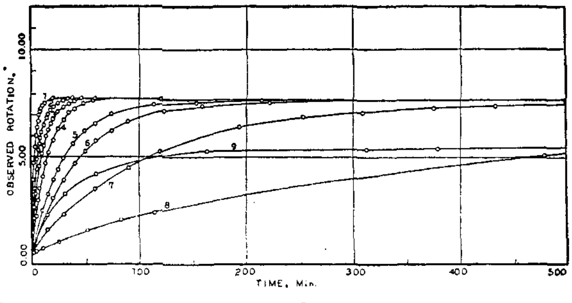
EFFECT OF β-D-GLUCOSE PENTAACETATE CONCENTRATION ON THE RATE OF ANOMERIZATION WITH 0.5 *M* SULFURIC ACID AT 25°

[β-D-Glucose pentaacetate] (mole/liter)	Solvent % Ac_2O	% AcOH	$k_1 + k_2$, min.$^{-1}$
0.05	100	0	0.502 ± 0.025
.10	100	0	.572 ± .017
.20	100	0	.472 ± .014
.05	50	50	.0356 ± .0002
.10	50	50	.0326 ± .0004
.20	50	50	.0362 ± .0001

Effect of Acetic Anhydride Concentration

The independence of the rate of anomerization on acetic anhydride concentration was established by using benzene as diluent. Within experimental error, $k_1 + k_2$ in pure acetic anhydride (0.273 ± 0.017 min.$^{-1}$) was the same as in a 50:50 mixture of benzene and acetic anhydride (0.294 ± 0.019 min.$^{-1}$). The insolubility of sulfuric acid in mixtures containing greater concentrations of benzene prevented the extension of these studies to such concentrations. Since even in the second experiment above the concentration of acetic anhydride is far larger than that of β-D-glucose pentaacetate, our studies have not permitted determination of the actual effect of acetic anhydride in low concentration on the rate of anomerization.

When acetic acid was used to dilute the acetic anhydride, the rate of anomerization decreased rapidly at first, then more gradually, with increasing acetic acid concentration. The relation between rate and composition of the solvent is illustrated in Fig. 3. Curve 9, obtained with pure acetic acid, will be discussed later.



Curve	1	2	3	4	5
% Ac_2O	100	90	80	70	50
% AcOH	0	10	20	30	50
$k_1 + k_2$, min.$^{-1}$	0.273	0.147	0.100	0.0662	0.0326

Curve	6	7	8	9
% Ac_2O	30	10	2.5	0
% AcOH	70	90	97.5	100
$k_1 + k_2$, min.$^{-1}$	0.0221	0.0095	0.0033	...

Fig. 3.—Effect of acetic acid concentration on the mutarotation of β-D-glucose pentaacetate.

The inhibiting effect of acetic acid on the rate is explainable as follows. As will be shown, the initiating step of the anomerization is the ionization of sulfuric acid in acetic anhydride, reaction (4). The conjugate acid, Ac_2OH^+, is believed responsible for causing anomerization at a rate, furthermore, directly proportional to its concentration. When acetic acid is present, it competes for the available sulfuric acid according to (5), thereby diminishing the concentration of the reactive ion, Ac_2OH^+, and retarding the rate. Experimental evidence for the basicity of acetic acid to sulfuric acid comes from its twofold freezing point depression with sulfuric acid.[14a]

If the basic nature of acetic acid to sulfuric acid is responsible for the inhibition, other substances basic to sulfuric acid should be similarly effective. Butyl ether has been employed to test this hypothesis. It was selected since solutions of β-D-glucose pentaacetate in mixtures of butyl ether, benzene and sulfuric acid showed only very slow mutarotation, indicating the probability of negligible side-reactions. Figure 4 and Table VII show that butyl ether acts in the same manner in retarding the rate of anomerization.

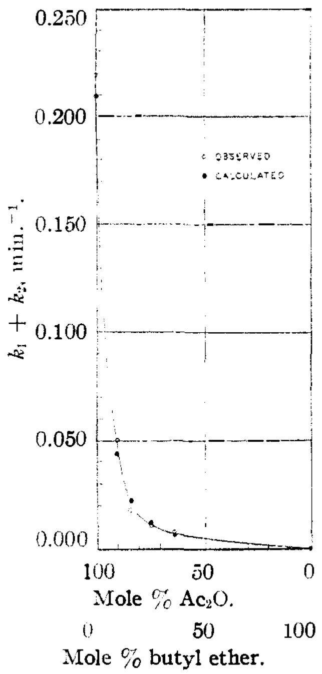


Fig. 4.—Effect of butyl ether on the rate of anomerization of β-D-glucose pentaacetate.

TABLE VII

EFFECT OF BUTYL ETHER ON THE RATE OF ANOMERIZATION OF β-D-GLUCOSE PENTAACETATE IN BENZENE–ACETIC ANHYDRIDE SOLUTIONS 0.363 *M* IN H_2SO_4 AT 25°

Mole % acetic anhydride[a]	Mole % butyl ether[a]	$k_1 + k_2$, min.$^{-1}$ Obsd.	Calcd.
100.0	0.0	0.219	0.209
90.6	9.4	.0503	.0438
84.4	15.6	.0179	.0211
75.0	25.0	.0114	.0123
64.2	35.8	.0079	.0075

[a] Based on $[Ac_2O]/([Ac_2O] + [\text{ether}])$.

Our suggestion regarding the cause of inhibition by these weak bases is susceptible to quantitative verification as follows. If both base and acetic anhydride compete instantaneously for a proton of sulfuric acid, (6) and (7) apply, where B is the weak base and *K* the equilibrium constant for reaction (6).

$$BH^+ + Ac_2O \rightleftarrows B + Ac_2OH^+ \qquad (6)$$

$$[Ac_2OH^+] = \frac{K[BH^+][Ac_2O]}{[B]} \qquad (7)$$

Since primary ionization of the sulfuric acid is complete, Equations (8), (9), and by development of (9), (10) follow

$$[Ac_2OH^+] + [BH^+] = [H_2SO_4] \qquad (8)$$

$$[Ac_2OH^+] = \frac{K[Ac_2O][H_2SO_4]}{[B]} - \frac{K[Ac_2O][Ac_2OH^+]}{[B]} \qquad (9)$$

$$[Ac_2OH^+] = \frac{K[Ac_2O][H_2SO_4]}{[B] + K[Ac_2O]} \qquad (10)$$

Now assuming the rate *R* (*i.e.*, $k_1 + k_2$) is proportional to $[Ac_2OH^+]$, we may write (11) relating the rate with the concentrations of acetic anhydride, base and catalyst.

$$R = \frac{kK[Ac_2O][H_2SO_4]}{[B] + K[Ac_2O]} \qquad (11)$$

Equation (11) develops to (12), where the subscripts 1 and 2 refer to measured rates and concentrations in two sets of experiments

$$K = \frac{R_1[Ac_2O]_2[B]_1 - R_2[Ac_2O]_1[B]_2}{[Ac_2O]_1[Ac_2O]_2(R_2 - R_1)} \qquad (12)$$

In using (12) to evaluate *K*, the equilibrium constant of reaction (6), it is convenient to select as one of the sets of data the experiment involving 100% acetic anhydride. Here $[B]_1 = 0$, and (12) reduces to (13)

$$K = \frac{-R_2[B]_2}{[Ac_2O]_2(R_2 - R_1)} \qquad (13)$$

Equation (13) was used to calculate *K* for each value of $k_1 + k_2$ in Table VII. Values of 0.0210, 0.0165, 0.0236 and 0.0183, respectively, were obtained at each point, with $K = 0.0198 \pm 0.0025$ as average. The proportionality constant, *k*, in Equation (11) was evaluated as 0.604 by employing data from the 100% acetic anhydride experiment (*i.e.*, $[B] = 0$; $[H_2SO_4] = 0.363$) in Equation (11).

Substituting *k* and the average value of *K*, obtained as above, into (11), and knowing $[Ac_2O]$, [butyl ether] and $[H_2SO_4]$, the effect of butyl ether at varying concentrations on the rate of anomerization was then calculated. Table VII and Fig. 4 indicate that the quantitative theory fits the experimental results with fair accuracy. The greatest source of disagreement in the experimental and theoretical points is probably "aging" which was rather marked in runs containing butyl ether.

A similar attempt to interpret quantitatively the inhibition by acetic acid was not as clean cut. The value of *K* for reaction (6), where B is now acetic acid, was not constant, but increased fourfold over the concentration range, mole % acetic acid 0 to 94. The anomerization thus appeared to go slightly faster than predicted with high concentrations of acetic acid. Possibly the dehydrating action of sulfuric acid converting some of the acetic acid to an

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(14) (a) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 46; (b) *ibid.*, p. 120.

unknown additional amount of acetic anhydride, or possibly the change to an increasingly more acidic medium[14b] is responsible for the anomalous results.

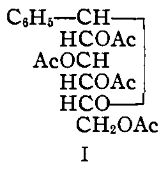
As predicted, dioxane also strongly retarded the anomerization. No attempt was made to treat this case quantitatively, however, since "aging" was particularly evident in these mutarotations.

Specificity of the Anomerization Process

While previous investigators have pointed out that anomerization is an equilibrium reaction, and while both anomers have sometimes been isolable from one of the pure components, it has never been demonstrated that limited side reactions do not also occur. Thus it has been assumed, but never proved, that the mutarotation of acetylated aldoses in acetic anhydride containing acid catalysts was due to a reaction specific only for the anomeric center. In order for our kinetic evidence to have mechanistic significance, it was necessary to demonstrate experimentally the validity of this assumption. We have gained such evidence from two sources.

When β-D-glucose pentaacetate was anomerized, the equilibrated product was isolable quantitatively. From the specific rotation of one such product, we estimated it to contain 83.5% α-, and 16.5% β-D-glucose pentaacetate. A synthetic mixture containing the two anomers in identical proportions was accordingly prepared, and the infrared spectra of the two samples compared. Figure 5 shows the spectra identical in every respect. The vertical displacement of the two curves is due to differing sample thicknesses. Since Kuhn has shown[15] the marked dependence of the infrared spectra of carbohydrates on structure, we may be reasonably certain that the anomerized product contains no appreciable amounts of other carbohydrate substances.

The stability of the ester linkages under anomerizing conditions was demonstrated as follows. Tetraacetyl-β-D-glucopyranosylbenzene (I)[16] was treated with propionic anhydride and sulfuric acid. No mutarotation was observed, and I was recoverable unchanged. Similarly, tetrapropionyl-β-D-glucopyranosylbenzene[17] in acetic anhydride and sulfuric acid led to no reaction. Since I differs from β-D-glucose pentaacetate only in its possession of phenyl instead of acetoxyl at the anomeric center, and since no mutarotation or acyl interchange in I was noted, the anomerization must clearly involve no structural change other than that at the anomeric center.



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Thermodynamic Considerations

Equilibrated products from previous mutarotations were isolated. Specific rotations varying randomly from $[\alpha]^{25}D$ 83.4° (chloroform) to 87.8° were obtained, with an average of 85.6 ± 1.0°. This gives an average composition for the equilibrated product of $\alpha:\beta$/83.5 ± 1.0: 16.5 ± 1.0, an equilibrium constant, K_e, for Equation (2) of 0.198 ± 0.014, and a figure of 960 cal./mole for the standard free energy of anomerization at 25°.

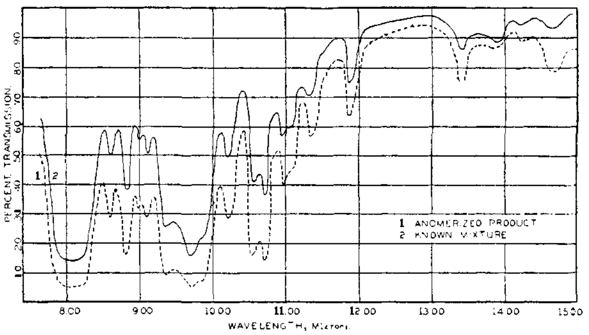

Fig. 5.—Comparison of infrared spectra of anomerized β-D-glucose pentaacetate with a known mixture of the anomers.

We have also studied the effect of temperature on the anomerization of β-D-glucose pentaacetate in 50:50 acetic anhydride–acetic acid, observing the temperature coefficient of both rate and equilibrium constants. Table VIII shows the effect over the range 0–33°. The K_e values were again obtained from the specific rotations of the isolated, anomerized products. The 50:50 solvent was selected for these studies since previous experience suggested that experimental irregularities due to aging or other factors were at a minimum in a solvent of this composition, and that thermodynamic calculations should have most reliability here.

TABLE VIII

EFFECT OF TEMPERATURE ON RATE AND EQUILIBRIUM CONSTANTS FOR THE ANOMERIZATION OF β-D-GLUCOSE PENTAACETATE IN 50:50 Ac_2O-AcOH, 0.1 M IN SULFURIC ACID

Temp., °K.	$k_1 + k_2$, min.$^{-1}$	K_e
273.1	0.00123 ± 0.00003	0.168
282.5	.00398 ± .0003	.184
290.8	.0153 ± .0006	.196
298.1	.0326 ± .0004	.214
306.1	.0852 ± .0009	(.222)[a]

[a] Calculated value.

A plot of log K_e *versus* $1/T$ forms a straight line whose slope gives 1385 cal./mole for ΔH^0, the heat absorbed for the reaction $\alpha \rightarrow \beta$ under standard conditions. It should be noted, however, that the individual values of K_e in Table VIII are practically all within the average deviations of K_e at 25°, so that our precision may be questionable. In any case, the heat of reaction is quite small. From our values of ΔF^0 and ΔH^0, we estimate ΔS^0 for the anomerization reaction to be 1.4 cal./mole° at 25°.

Knowing the quantities ($k_1 + k_2$) and K_e, and the fact that $K_e = k_1/k_2$, it is possible to calculate the individual rate constants k_1 and k_2 at each temperature (Table IX). Plotting the logarithms of k_1 and k_2, respectively, against $1/T$ gave straight lines from whose slopes ΔH_1^* and ΔH_2^*, the activation energies of the forward and reverse transformations, were calculated. The activation energy for the reaction $\alpha \rightarrow \beta$ proved to be 22,500 cal./mole, while that for the reaction $\beta \rightarrow \alpha$ was 21,000 cal./mole.

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[15] Kuhn, *Anal. Chem.*, **22**, 276 (1950).

[16] Hurd and Bonner, THIS JOURNAL, **67**, 1664, 1759, 1972 (1945).

[17] Bonner and Koehler, *ibid.*, **70**, 314 (1948).

Using the standard equation, rate = $PZe^{-\Delta H^*/RT}$, we estimate that the PZ term for the forward reaction is 1.77 × 10^{14} min.$^{-1}$ and for the reverse reaction 7.98 × 10^{13} min.$^{-1}$. It is interesting that these PZ values are of identical magnitude with those obtained in simple gas phase reactions. We have further calculated the standard entropies and free energies of activation for the forward and reverse processes. For the forward process, ΔS_1^* comes out at 6.8 cal./mole^0 and ΔF_1^* as 20,480 cal./mole. For the reverse process ΔS_2^* is 5.1 cal./mole^0 and ΔF_2^* 19,580 cal./mole.

TABLE IX

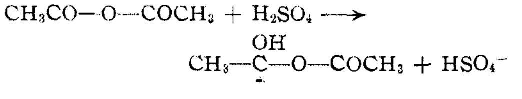
INDIVIDUAL RATE CONSTANTS AS A FUNCTION OF TEMPERATURE IN 50:50 Ac_2O–AcOH 0.1 M IN SULFURIC ACID

Temp., °K.	k_1, min.$^{-1}$	k_2, min.$^{-1}$
273.1	0.000177	0.00105
282.5	.000618	.00336
290.8	.00251	.0128
298.1	.00575	.0269
306.1	.0155	.0697

A Mechanism for Anomerization

Only glucose pentaacetate, acetic anhydride and the acid catalyst appear involved in anomerization. Thus β-D-glucose pentaacetate fails to mutarotate without catalyst. Similarly, acetic acid is probably not involved since (a) the reaction is most rapid in its absence, and (b) while β-D-glucose pentaacetate in acetic acid shows an acid-catalyzed mutarotation (Fig. 3) the product is an indistinct sirup rather than the crystalline mixture obtained with acetic anhydride. A mechanistic proposal should accord with these facts, as well as the previously discussed kinetics, general acid catalysis, absence of salt effect, inhibition by inert bases, and specificity for the anomeric center. Several mechanisms appear to meet most or all of these criteria, and we have unfortunately no experimental criteria for preference. The mechanism briefly proposed below rationalizes the known experimental facts, and appears to us a logical possibility.

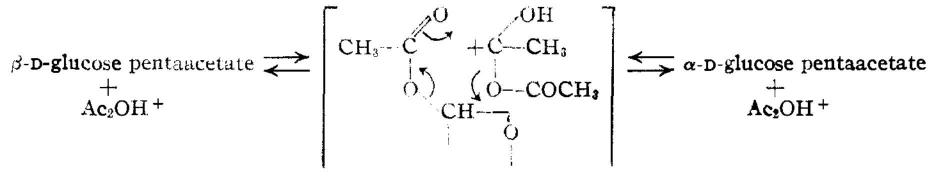
The first step is the instantaneous, complete ionization of sulfuric acid in acetic anhydride, reaction (14).



$$CH_3CO—O—COCH_3 + H_2SO_4 \longrightarrow \underset{+}{\overset{OH}{CH_3—C—}}O—COCH_3 + HSO_4^- \quad (14)$$

The carbonyl oxygen in the anhydride should be more basic, since the conjugate acid in (14) may be stabilized by more singly charged contributing resonance structures than the alternative, $CH_3CO—\underset{+}{\overset{OH}{C}}—COCH_3$. The rapidity of (14) is suggested by instantaneous warming on mixing the components, and the complete ionization by the absence of an anomerization rate retardation on adding bisulfite.

The rate determining second stage in the reaction may be the attack of the conjugate acid in (14) on the anomeric acetoxy group of D-glucose pentaacetate, giving one or more resonance stabilized intermediates (IIa) which then decompose either to the reactants or, with inversion, to the products.



(15)

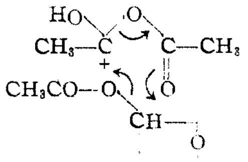
IIa

Development of the kinetic equations applying to (15) leads to (16) as the integrated rate expression describing the anomerization.

$$K = \frac{1}{[Ac_2OH^+]} \times \frac{2.303}{t} \times \log\frac{R_0 - R_e}{R_t - R_e} \quad (16)$$

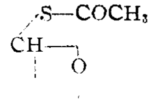
In view of the irreversibility of (14), it is clear that the theoretically derived Equation (16) is completely equivalent to the empirically observed Equation (3), and that mechanism (15) is in accord with the observed kinetics.

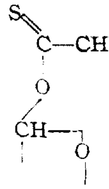
An alternative method of writing IIa is IIb, where the ester oxygen rather than the carbonyl oxygen of the acetoxy group attacks the conjugate acid. We have attempted to determine the



IIb

preferred mode of attack, IIa or IIb, by using acetyl sulfide in place of acetic anhydride. If IIa were preferred IIIa should result, while IIb would give IIIb.



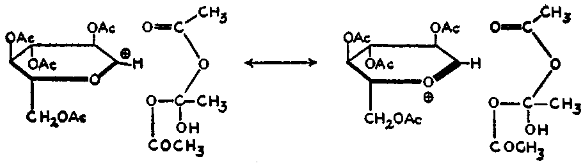


IIIa IIIb

The structure of the product might be determined by reductive desulfurization, IIIa giving tetraacetyl-1,5-anhydro-D-glucitol, and IIIb ethyl tetraacetyl-α-D-glucoside. β-D-Glucose pentaacetate, however, failed to react with acetyl sulfide and sulfuric acid and, even at 100°, was recovered unchanged. Similarly, pentaacetyl-1-thio-β-D-glucose, the anomer of IIIa, failed to react with acetic anhydride and sulfuric acid, suggesting that anomerization cannot occur if a hetero sulfur atom is involved in the intermediates IIa or IIb.

With anhydrides other than acetic anomerization occurred with replacement of the anomeric acetoxy group, as Equation (15) predicts. β-D-Glucose pentaacetate, sulfuric acid and propionic anhydride gave strong dextro-mutarotation, and 1-propionyl-2,3,4,6-tetraacetyl-α-D-glucose was isolated. The latter with sulfuric acid and acetic anhydride gave weak levo-mutarotation and α-D-glucose pentaacetate. Similarly, 1-propionyl-2,3,4,6-tetraacetyl-β-D-glucose, sulfuric acid and acetic anhydride gave strong dextro-mutarotation and α-glucose pentaacetate.

The specificity of the anomerization process for anomeric acetoxy group is in line with the general greater reactivity of sugars at C-1. In terms of the present mechanism this might be interpreted as resulting from extra resonance stabilization by structure IVb, which is not possible at the remaining acetoxy groups.



IVa IVb

While the proposed mechanism accords with all kinetic and chemical facts regarding the anomerization, the data may justify alternative interpretations. However, in view of the ease of formation, stability and prevalence of six-membered rings in nature, we feel that a cyclic six-membered intermediate provides the most logical and attractive mechanistic hypothesis when theoretically possible and not experimentally precluded.

Experimental

Anomerizations of D-Glucose Pentaacetates.—The data in Tables I through VII were obtained in the following manner. The D-glucose pentaacetate (0.3900 g., 0.001 mole) was dissolved in 4 ml. of the solvent mixture (containing the indicated quantities of acetic anhydride and diluent). The calculated volume of C.P. sulfuric acid was added to 4 ml. of the solvent mixture and the solution cooled. The two solutions were mixed in a 10-ml. volumetric flask, the stop-watch started, and the contents brought to the mark with solvent. The mixture was transferred rapidly to a jacketed, all-glass, 2 dcm. polarimeter tube, through whose jacket water at 25.0 ± 0.1° was pumped from a thermostat. The contents were mixed by inverting the tube several times, and the initial polarimetric reading taken. The time elapsed before the first reading was about one minute. Between ten and twenty readings were taken at arbitrary times until mutarotation stopped. Zero time readings were obtained either by extrapolation or by observing an identical reaction mixture lacking the catalyst. The two methods gave concordant results. Rate values were obtained at each reading of rotation and time by the use of Equation (1), and the averages of these values included in the tables. In cases where "aging" was evident the later values were discarded. Rate values as a function of temperature (Table VIII) were obtained in the same way, except that the component solutions were brought to temperature before mixing.

After completion of mutarotation, the reaction mixtures were thrown into water and the solutions extracted with chloroform. The extracts were washed with water and saturated bicarbonate solution, then dried over sodium sulfate, filtered, and the solvent distilled *in vacuo*. The residues were dried over phosphoric anhydride *in vacuo*, weighed, and the specific rotations determined in chloroform. In the majority of cases, the recovery of anomerized D-glucose pentaacetate was practically quantitative.

Infrared Spectrum.—β-D-Glucose pentaacetate (1.00 g.) was dissolved in acetic anhydride (15 ml.), and a solution of sulfuric acid (0.8 ml.) in acetic anhydride (5 ml.) added. The mixture stood for one hour and was poured into ice-water. After 20 minutes the solution was extracted with absolute ether, and the extract washed and dried as usual. Removal of the ether left a white solid weighing 0.81 g. after drying over phosphoric anhydride *in vacuo*. This had $[\alpha]^{20}D$ 85.8° (*c*, 2.693, chloroform), and corresponded to a mixture of 83.5% α- and 16.5% β-D-glucose pentaacetate.

A synthetic mixture containing 0.8350 g. α- and 0.1650 g. β-D-glucose pentaacetate was prepared by intimate grinding and shaking. This had $[\alpha]^{20}D$ 84.8° (*c*, 3.342, chloroform).

The infrared spectrum of each sample was determined according to the procedure of Kuhn,[15] using a suspension of the sample in mineral oil. The region 7.5 to 15 μ was covered using a Perkin–Elmer infrared spectrophotometer. The results appear in Fig. 5. The author is indebted to Dr. John H. Wise for these measurements.

Attempted Transacylation of Tetraacetyl-β-D-glucopyranosylbenzene (I).—Tetraacetyl-β-D-glucopyranosylbenzene (0.408 g.) was dissolved in propionic anhydride (10 ml.) and sulfuric acid (0.279 ml.) added. The rotation in a 2 dcm. tube was −1.06° at the start and −0.97° after 16 hours. The crude product was isolated as above and had m.p. 150–151°. It showed m.p. 151–153.5° when mixed with pure starting material (m.p. 155°).

Attempted Transacylation of Tetrapropionyl-β-D-glucopyranosylbenzene.—Tetrapropionyl-β-D-glucopyranosylbenzene (0.232 g.) was dissolved in acetic anhydride (10 ml.) and sulfuric acid (0.279 ml.) added. The mixture showed no mutarotation during 390 minutes, and the product was isolated in 78% yield as before. The crude material had m.p. 64–66° and showed no depression (66–67°) when mixed with pure starting material (m.p. 69.5°).

1-Propionyl-2,3,4,6-tetraacetyl-α-D-glucose.—β-D-Glucose pentaacetate (1.00 g.) was dissolved in propionic anhydride (10 ml.) and sulfuric acid (0.5 ml.) added. The rotation of the solution increased from 4.64° at 1.5 minutes to 17.75° after about an hour. The mixture was thrown into water, stirred an hour, and extracted with ether. Customary washing of the extract followed by evaporation gave a sirup. This could be crystallized from a mixture of 2-propanol and petroleum ether to give 0.40 g. of crude product, m.p. 67–68°.

Repeated on a tenfold scale, the product crystallized during hydrolysis of the excess anhydride. It was filtered, rinsed with water, and dried to give 5.40 g. of white solid, m.p. 71.5–72°. After five recrystallizations from a mixture of 2-propanol and petroleum ether the substance had m.p. 72–73° and $[\alpha]^{22}D$ 95.0° (*c*, 0.927, chloroform).

Anal. Calcd. for $C_{17}H_{24}O_{11}$: C, 50.55; H, 5.98. Found: 50.70, 50.75; H, 5.96, 5.99.

1-Propionyl-2,3,4,6-tetraacetyl-β-D-glucose.—Tetraacetyl-α-D-glucosyl bromide (8.22 g.) was dissolved in chloroform (50 ml.), and a solution of potassium hydroxide (1.24 g., 10% excess) and propionic acid (1.59 ml., 10% excess) in ethanol (15 ml.) was added. The mixture was refluxed for seventy minutes, cooled, and washed thrice with water. On drying and removing solvent, 8.20 g. of a colorless sirup resulted. This was crystallized from a mixture of 2-propanol and petroleum ether at 0° to produce 5.25 g. of white needles, m.p. 81–83°. After nine recrystallizations from the same solvent the substance had m.p. 97–97.5° and $[\alpha]^{25}D$ in chloroform was zero.

Anal. Calcd. for $C_{17}H_{24}O_{11}$: C, 50.55; H, 5.98. Found: C, 50.62, 50.72; H, 5.99, 5.94.

Acetic Anhydride, Sulfuric Acid and 1-Propionyl-2,3,4,6-tetraacetyl-β-D-glucose.—1-Propionyl-2,3,4,6-tetraacetyl-β-D-glucose (0.39 g.) in acetic anhydride (4 ml.) was treated with acetic anhydride (5 ml.) containing sulfuric acid (0.55 ml.). The mixture was brought to the 10.0 ml. mark and placed in a 2 dcm. polarimeter tube. The rotation (4.50° after one minute) was constant at 7.54° after 13 minutes. After 30 minutes the product was isolated in the usual way. An amber sirup (0.40 g.) was obtained, which crystallized spontaneously. After thorough desiccation, this had $[\alpha]^{25}D$ 83.7° (*c*, 0.490, chloroform). Recrystallized twice from 2-propanol the product had $[\alpha]^{20}D$ 101.4° (*c*, 0.857, chloroform), m.p. 111–112°, mixed m.p. with α-D-glucose pentaacetate 110.5–111.5°.

Acetic Anhydride, Sulfuric Acid and 1-Propionyl-2,3,4,6-tetraacetyl-α-D-glucose.—The α-anomer (0.39 g.) was treated as the β-anomer above. The rotation (8.49° after one minute) was constant at 8.07° after 20 minutes. After 70 minutes the product was isolated as before, resulting in

0.33 g. of clear sirup which crystallized spontaneously. Its rotation was $[\alpha]^{20}\mathrm{D}$ 83.8° (*c*, 1.05, chloroform). Two recrystallizations from 2-propanol gave almost pure α-D-glucose pentaacetate, m.p. 108°, mixed m.p. 109–111°.

Pentaacetyl-1-thio-β-D-glucose.—Tetraacetyl-α-D-glucosyl bromide (4.11 g.) in chloroform (30 ml.) was treated with a mixture of potassium hydroxide (0.62 g., 10% excess) and thioacetic acid (0.9 ml., 10% excess) in ethanol (5 ml.). The solution was refluxed for 30 minutes, cooled and the potassium bromide (0.95 g.) filtered. The filtrate was washed as usual, dried and evaporated to give 3.92 g. of crude, amber, sirup. This was crystallized, with Norit decolorization, from a mixture of 2-propanol and petroleum ether to give white needles, m.p. 116–117°. After two further recrystallizations from 2-propanol the product had m.p. 118° and $[\alpha]^{21}\mathrm{D}$ 10.7° (*c*, 1.496, chloroform).

Anal. Calcd. for $C_{16}H_{22}O_{10}S$: C, 47.40; H, 5.47; S, 7.89. Found: C, 47.27, 47.34; H, 5.49, 5.41; S, 7.88, 7.83.

This product, prepared by more cumbersome methods, has been previously reported[18] to have m.p. 120° or 121° and $[\alpha]^{22}\mathrm{D}$ 10.17° (tetrachloroethane).

Reductive Desulfurization of Pentaacetyl-1-thio-β-D-glucose.—Pentaacetyl-1-thio-β-D-glucose (2.5 g.) was refluxed in absolute ethanol (*ca.* 40 ml.) containing Raney nickel (*ca.* 15 g.) for 3.5 hours. The mixture was cooled, filtered (Celite), and evaporated in an air stream to a volume of several ml. The residue was dissolved in ether, and the solution washed with water, dried over anhydrous sodium sulfate, filtered and the solvent distilled, leaving 1.38 g. (68%) of clear sirup. This was dissolved in a few ml. of dry ether, treated with isopentane to incipient turbidity, and seeded with tetraacetyl-1,5-anhydro-D-glucitol.[19] On standing at 0° the solution produced 0.70 g. of white needles, m.p. 68–69°. These were recrystallized from the same solvent mixture to produce a sample of m.p. 72.5°. This had $[\alpha]^{21}\mathrm{D}$ 38.8° (*c*, 0.567, chloroform), and showed no mixed melting point depression with authentic tetraacetyl-1,5-anhydro-D-glucitol.[19]

Acetyl Sulfide, Sulfuric Acid and β-D-Glucose Pentaacetate.—Acetyl sulfide[20] (5 ml.) was treated with sulfuric acid (0.5 ml.) and the mixture, smelling somewhat of sulfur dioxide, filtered through Celite. β-D-Glucose pentaacetate (1.00 g.) was dissolved in acetyl sulfide (5 ml.), and the two solutions mixed. No significant change in the rotation of the mixture was noticed during 18 hours. The mixture was accordingly heated on the steam-bath for 20 hours. The dark solution was cooled, neutralized with sodium hydroxide solution, and steam distilled. On cooling, the residue (*ca.* 100 ml.) deposited 0.70 g. of yellow solid, m.p. 128–130°. After two recrystallizations from 2-propanol, the product had m.p. 131°, and showed no mixed m.p. depression with the starting material.

Acetic Anhydride, Sulfuric Acid and Pentaacetyl-1-thio-β-D-glucose.—Pentaacetyl-1-thio-β-D-glucose (1.00 g.) in acetic anhydride (10 ml.) containing sulfuric acid (0.3 ml.) gave a solution whose rotation changed only from 0.87 to 0.98° in 8.5 hours in a one decimeter tube. The solution was poured into water, extracted with ether, and processed as usual to give 0.70 g. of starting material, m.p. and mixed m.p. 118°.

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[18] Vogel and George, "Tabellen der Zucker und Ihrer Derivate," Julius Springer, Berlin, 1943, p. 252.

[19] The seed was obtained through the kindness of Dr. H. G. Fletcher, Jr.

[20] Bonner, THIS JOURNAL, **72**, 4270 (1950).

STANFORD, CALIFORNIA RECEIVED JULY 10, 1950

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

Studies of Cation-exchange Equilibrium on a Synthetic Resin[1,2]

BY WARREN K. LOWEN, RAYMOND W. STOENNER, WILLIAM J. ARGERSINGER, JR., ARTHUR W. DAVIDSON AND DAVID N. HUME

Eight exchange systems on Dowex 50 have been investigated, involving the ions Na^+, H^+, NH_4^+, Ag^+, Tl^+, Ni^{++} and Ca^{++} in solutions of total ionic strength of approximately unity. Equivalence of exchange, as ordinarily understood, is not obtained in these systems. The apparent discrepancies between the decrease in concentration of one ion in the solution and the increase in concentration of another almost certainly arise mainly from the absorption of water by the resin. In certain systems, especially those involving either silver or thallous ion, adsorption of electrolyte by the resin occurs also.

The effect of the nature of the anion in solution on the exchange equilibrium has been found to be negligible, and hysteretic effects, in all but a very few cases, are only apparent. In every exchange system studied, the apparent equilibrium constant has been found to vary regularly with the equilibrium resin composition. Since the error involved in the assumption of constant activity coefficient ratios in the aqueous solution is presumably slight, it is concluded from this variation in equilibrium quotient that the common assumption of ideal solid solution behavior in the resin phase must be invalid.

Introduction

Although attempts have been made to formulate heterogeneous cation-exchange equilibria in terms both of the Langmuir adsorption mechanism[3] and of the Donnan membrane equilibrium,[4] the most fruitful theoretical treatments of such equilibria have been those based upon the application of the law of chemical equilibrium to the exchange, regarded as a simple metathetical reaction.[3–7]

Thus, in the simplest case, when both of the cations are univalent, let us consider the reaction to be that represented by the equation

$$A^+ + BR = B^+ + AR$$

where A^+ and B^+ are the cations involved in the exchange and R represents the active anionic portion of the insoluble resin. From a purely thermodynamic viewpoint, then, and regardless of the structure of the resin, the following equation should be applicable

$$\frac{a_{B^+}a_{AR}}{a_{A^+}a_{BR}} = K_a \qquad (1)$$

where a_{A^+}, a_{B^+}, a_{AR} and a_{BR} are the activities of the respective ions in the solution and of the two resin

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(1) Abstracted from independent Ph.D. theses by W. K. Lowen and R. W. Stoenner, University of Kansas, 1949. This material was presented at the 115th Meeting of the American Chemical Society, April, 1949, and is contained also in a report to the Office of Naval Research, NR057158, August, 1950.

(2) For detailed tables of data supplementary to this article, order Document 3122 from American Documentation Institute, 1719 N Street, N. W., Washington 6, D. C., remitting \$1.00 for microfilm (images 1 inch high on standard 35 mm. motion picture film) or \$2.25 for photocopies (6 × 8 inches) readable without optical aid.

(3) G. E. Boyd, J. Schubert and A. W. Adamson, THIS JOURNAL, **69**, 2818 (1947).

(4) W. C. Bauman and J. Eichhorn, *ibid.*, **69**, 2830 (1947).

(5) W. Juda and M. Carron, *ibid.*, **70**, 3295 (1948).

(6) J. F. Duncan and B. A. J. Lister, *J. Chem. Soc.*, 3285 (1949).

(7) J. A. Marinsky, *Technical Report*, NR26001 (1949).