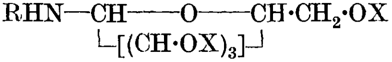
CCLIX.—*The Mechanism of Tautomeric Interchange and the Effect of Structure on Mobility and Equilibrium. Part III. The Function of Alkaline and Acid Catalysts in the Mutarotation of some Derivatives of Tetramethyl Glucose.*

By JOHN WILLIAM BAKER.

IN Part II (this vol., p. 1583) it was shown that catalysts which facilitate the prototropic change involved in the mutarotation of sugars may be of two kinds : (*a*) those which attack the ionising proton directly, and (*b*) those which facilitate its liberation indirectly. Experiments on the relative velocity of mutarotation of a series of nitrogen derivatives of tetra-acetyl glucose of type I (X = Ac) suggested that acids, which fall within the second category



$$\begin{array}{l}\mathrm{RHN{-}CH{-\!-}O{-\!-}CH{\cdot}CH_2{\cdot}OX}\\ \quad\;\llcorner[(\mathrm{CH{\cdot}OX})_3]\lrcorner\end{array}$$

(I.)

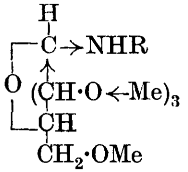
of catalysts, function by inducing a positive charge on the nitrogen atom, which in turn facilitates the liberation of the attached proton. Unfortunately, in this series of sugar derivatives a study of the action of catalysts of the first type, of which alkalis are an example, is rendered difficult by the tendency of the acetyl groups to hydrolysis. Such an investigation is, however, possible in the case of the corresponding derivatives of tetramethyl glucose, and this communication deals with the effect of acid and alkaline catalysts on the relative velocities of mutarotation of a series of *p*-substituted anilides of tetramethyl glucose (type I, X = Me) (prepared by the direct interaction of the sugar and the base) when the group R is varied. With acid catalysts, it is again found, as is the case in the corresponding tetra-acetyl derivatives, that, as the group R is varied, the velocity of the mutarotation runs parallel with the strengths as bases of the compounds RNH_2, *viz.*,

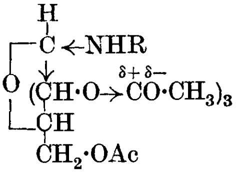
$$-C_6H_4\cdot OMe(p) > -C_6H_4Me(p) > -C_6H_5 > -C_6H_4Cl(p) > -C_6H_4Br(p)$$

a sequence which is in agreement with the prediction based on the mechanism previously suggested, but opposed to that required by the extension of a duplex theory (Part II, *loc. cit.*).

The solvent * used was one in which a determination of the velocities of mutarotation of three of the corresponding derivatives of tetra-acetyl glucose had already been made, and hence data are now available for a comparison of the effect, on the velocity of mutarotation, of structural changes in the non-tautomeric glucose portion of the molecule. By analogy with the known effect of the acetyl group in diminishing, and of the methyl group in increasing, the basic character of the nitrogen atom in $NHR\rightarrow \overset{\delta+\,\delta-}{CO}\cdot CH_3$ and $NHR\leftarrow Me$, it would be expected that the anilides of tetramethyl glucose (A) would be more basic in character than the corresponding derivatives of tetra-acetyl glucose (B),

(A.)





(B.)

and hence, under identical conditions of acid catalysis, the velocity of mutarotation of derivatives of the former should be greater than that of corresponding derivatives of the latter. The experimental results given below, which refer to the velocity of mutarotation in a 0·9*N*-solution of acetic acid in ethyl acetate at 25°, are in agreement with this prediction.

Mutarotation of p-*substituted anilides in* 0·9N-*acetic acid in ethyl acetate at* 25°.

	Unimolecular velocity coefficient (hr.$^{-1}$).	
R.	(*a*) Derivatives of tetramethyl glucose.	(*b*) Derivatives of tetra-acetyl glucose.
C_6H_4Br	0·39	—
C_6H_4Cl	0·46	—
C_6H_5	1·30	0·21
C_6H_4Me	4·12	0·58
$C_6H_4\cdot OMe$	12·0	1·69

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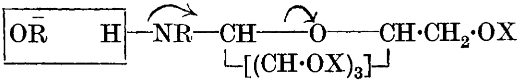
* Pure, acid-free ethyl acetate (but not an arrest sample) was used in the preparation of the solution; but the *same* solution was used throughout, since the object was merely to obtain constant catalytic conditions.

The results obtained for alkaline catalysis are more complicated and their interpretation much less clearly defined than in the case of acid catalysis. It would be expected that the primary function of alkaline catalysts, which are included in the first class, would be the direct attack of the ionising proton of the sugar molecule by the negative ion of the catalyst in accordance with the scheme



$$\boxed{O\bar{R}\quad H}-\overset{\frown}{NR}-\underbrace{CH-\overset{\frown}{O}-CH}_{[(CH\cdot OX)_3]}\cdot CH_2\cdot OX$$

Other structural and experimental conditions being equal, the velocity of mutarotation based on this mechanism will depend on the relative ease with which the H of the –NHR group can separate as a proton. This, in turn, as indicated in Part II, will depend on the extent to which the group R collaborates with the catalyst proton acceptor. Approximate data of the order of this effect may be obtained from the relative strengths as acids of the compounds $R{\cdot}CO_2H$ or $R{\cdot}OH$. This for the series of *p*-substituted anilides studied is

$$(-C_6H_4Br,\ -C_6H_4Cl) > -C_6H_5 > -C_6H_4Me > -C_6H_4{\cdot}OMe.$$

On the other hand, experimentally it is difficult completely to eliminate catalysts of the second type, such as water and possibly alcohol, which may function in an indirect manner by a mechanism analogous to that shown to exist in the case of catalysis by acids, *viz.*, by inducing a fractional positive charge on the nitrogen atom. Such catalytic action would be most effective with the derivative of the strongest base, the sequence in the series under consideration being that given for acid catalysis on p. 1980. Therefore in alkaline catalysis it seems probable that at least two different types of mechanism may function, one of which is most powerful with the derivative of the weakest base, the other reaching its maximum with the derivative of the strongest base. The superimposition of these two mechanisms may therefore lead to the existence of a minimum value for the velocity of mutarotation at some intermediate point in the series. This theory is tentatively suggested as one satisfactory explanation of the experimental results obtained. These refer to the mutarotation of a series of *p*-substituted anilides of tetramethyl glucose in ether containing a small concentration of an alcoholic solution of sodium ethoxide. In the first two series of experiments, the concentration of sodium ethoxide was approximately 0·0006*N*, and a small (constant but undetermined) quantity of water was present. The values of the unimolecular velocity coefficients of the various derivatives at 25° are as follows: $-C_6H_4Cl$, 1·33; $-C_6H_4Br$, 1·24; $\underset{\text{(minimum)}}{-C_6H_5,\ 1{\cdot}13}$; $-C_6H_4Me$, 1·21; $-C_6H_4{\cdot}OMe$, 2·41 ($hr.^{-1}$). In this series a minimum value for the velocity coefficient is found in the case of the unsubstituted anilide.

With the object of accelerating the direct mechanism and impeding the indirect type of catalytic action, another series of experiments was carried out in which a higher proportion (0·001*N*) of sodium ethoxide was used, and in which water was rigidly excluded. These measures were calculated to shift the position of the minimum velocity to the right in the above series, so that a greater number of the derivatives would fall into the sequence demanded by the direct mechanism alone (p. 1981). The following experimental values of the unimolecular velocity coefficients confirm this expectation:

$$-C_6H_4Cl,\ 11{\cdot}4;\ -C_6H_4Br,\ 9{\cdot}1;\ -C_6H_5,\ 7{\cdot}7;\ \underset{\text{(minimum)}}{-C_6H_4Me,\ 6{\cdot}1};\ -C_6H_5{\cdot}OMe,\ 14{\cdot}7.$$

EXPERIMENTAL.

I. *Preparation of* p-*Substituted Anilides of Tetramethyl Glucose.*—These were prepared by boiling a mixture of tetramethyl glucose with an excess of the appropriate base in alcoholic solution for several hours in accordance with the method used by Irvine and Gilmour (J., 1908, **93**, 1440) for the preparation of the anilide.

p-*Bromoanilide*, after crystallisation from methyl alcohol, has m. p. 154° (Found: C, 48·8; H, 6·1. $C_{16}H_{24}O_5NBr$ requires C, 49·2; H, 6·2%).

p-*Chloroanilide*, after crystallisation from methyl alcohol–ligroin (b. p. 60—80°), has m. p. 141° (Found: C, 55·3; H, 7·0. $C_{16}H_{24}O_5NCl$ requires C, 55·5; H, 7·0%).

p-*Toluidide*, after crystallisation from absolute alcohol, has m. p. 151° (Found: C, 62·7; H, 8·0. $C_{17}H_{27}O_5N$ requires C, 62·8; H, 8·4%).

p-*Anisidide*, after crystallisation from ether–ligroin (b. p. 40—60°), has m. p. 110° (Found: C, 59·8; H, 8·0. $C_{17}H_{27}O_6N$ requires C, 59·8; H, 8·0%).

The anilide had m. p. 135° (Found: C, 61·7; H, 8·0. Calc.: C, 61·7; H, 8·1%).

II. *Relative Velocity Experiments.*—(A) *With acid catalysts.* The solution employed was one previously used in the determination of the relative velocities of mutarotation of the corresponding derivatives of tetra-acetyl glucose, and consisted of pure ethyl acetate to which acetic acid in a concentration 0·9*N* had been added (see footnote, p. 1980).

All polarimetric measurements were carried out in a 2-dcm. silica polarimeter tube with optically ground silica endplates fused on. The tube was jacketed for temperature control, the temperature readings recorded being those of the jacket. Measurements were made on the mercury green line, the light source being a powerful Kelvin, Bottomley, and Baird mercury vapour lamp. The velocity determinations were carried out consecutively, each series being completed within a few days in order to avoid any possibility of change in the composition of the solvent during a series of comparative experiments.

The value of $[\alpha]_0$ was determined by extrapolation to zero time of the straight line obtained by plotting log $([\alpha]_0 - [\alpha]_\infty)$ against time. Details of the polarimetric measurements are given only in the first set of each series.

Mutarotation of tetramethyl glucose anilides in a 0·9N-*solution of acetic acid in ethyl acetate at* 25°.

(*a*) *p*-Bromoanilide. Strength of solution = 0·9856 g./100 c.c. (0·025 g.-mol./l.).

$$[\alpha]_D = 245°. \quad k = \frac{2\cdot3}{t}\log\frac{[\alpha]_\infty - [\alpha]_0}{[\alpha]_\infty - [\alpha]_t}(\text{hr.}^{-1}).$$

t (hrs.).	α.	$[\alpha]_{5461}$.	k.	t (hrs.).	α.	$[\alpha]_{5461}$.	k.
0·084	4·73°	240·0°	0·384	1·75	3·33°	168·9°	0·405
0·166	4·64	235·4	0·388	2·25	3·07	155·8	0·402
0·25	4·55	230·8	0·386	3·34	2·66	135·0	0·397
0·417	4·36	221·2	0·408	4·0	2·49	126·3	0·393
0·50	4·28	217·1	0·409	5·25	2·25	114·2	0·394
0·75	4·09	207·5	0·380	6·34	2·09	106·0	—
1·0	3·89	197·3	0·382	8·17	1·99	101·0	—
1·25	3·68	186·7	0·392	11·75	1·88	95·4	—
1·50	3·51	178·1	0·392	∞	1·88	95·4	—
						Mean	0·394

(*b*) p-*Chloroanilide.* Strength of solution, 0·8656 g./100 c.c. (0·025 g.-mol./l.). $[\alpha]_0 = 268°$. $[\alpha]_\infty = 100·5°$.

Mean value of k (12 observations) = 0·464 hr.$^{-1}$ (max., 0·485; min., 0·445).

(*c*) *Anilide.* Strength of solution, 0·7808 g./100 c.c. (0·025 g.-mol./l.). $[\alpha]_0 = 285°$. $[\alpha]_\infty = 106°$.

Mean value of k (10 observations) = 1·30 hr.$^{-1}$ (max., 1·37; min., 1·25).

(*d*) p-*Toluidide.* Strength of solution, 0·8256 g./100 c.c. (0·025 g.-mol./l.). $[\alpha]_0 = 272°$. $[\alpha]_\infty = 110°$.

Mean value of k (11 observations) = 4·12 hr.$^{-1}$ (max., 4·18; min., 4·04).

(*e*) p-*Anisidide.* Strength of solution, 0·7408 g./100 c.c. (0·025 g.-mol./l.). $[\alpha]_0 = 279°$. $[\alpha]_\infty = 107°$.

Mean value of k (8 observations) = 12·1 hr.$^{-1}$ (max., 12·8; min., 11·6).

Summary of Acid Catalysis.

p-Substituent.	No. of mols. of anilide per litre.	Dissociation constant, K_b, of *p*-substituted aniline as a base.	Unimolecular velocity coefficient, *k*.	k/K_b.
Br	0·025	$1\cdot0 \times 10^{-10}$	0·39	$0\cdot39 \times 10^{10}$
Cl	,,	$1\cdot5 \times 10^{-10}$	0·46	$0\cdot31 \times 10^{10}$
H	,,	$4\cdot6 \times 10^{-10}$	1·30	$0\cdot28 \times 10^{10}$
Me	,,	$11—15 \times 10^{-10}$	4·12	$0\cdot38 \times 10^{10}$
OMe	,,	15×10^{-10}	12·1	$0\cdot77 \times 10^{10}$

(B) *With alkaline catalysts. Series I and II.*

Preparation of solution. A 0·1*N*-solution of sodium ethoxide in alcohol was prepared by addition of the required quantity of sodium to absolute alcohol (calcium-dried). 1·5 C.c. of this solution were added to about 246 c.c. of sodium-dried ether, and the solution made up to 250 c.c. by addition of ordinary absolute alcohol (99·5%) to keep the sodium ethoxide in solution. The solution was therefore approximately 0·0006*N* in sodium ethoxide.

Mutarotation of tetramethyl glucose anilides in an approximately 0·0006N-solution of sodium ethoxide in ether at 25°.

(*a*) *Anilide.* Strength of solution = 0·9976 g./100 c.c. $[\alpha]_0 = 274°$.

$$[\alpha]_\infty = 163°. \quad k = \frac{2\cdot3}{t}\log\frac{[\alpha]_\infty - [\alpha]_0}{[\alpha]_\infty - [\alpha]_t}.$$

t (hrs.).	α.	$[\alpha]_{5461}$.	*k*.	*t* (hrs.).	α.	$[\alpha]_{5461}$.	*k*.
0·067	5·32°	266·6°	1·036	1·17	3·84°	192·5°	1·134
0·167	5·12	256·5	1·033	1·75	3·56	178·4	1·125
0·334	4·78	239·6	1·109	2·25	3·43	171·9	1·106
0·417	4·64	232·6	1·120	3·0	3·33	166·9	—
0·5	4·51	226·0	1·131	6·0	3·25	162·9	—
0·666	4·30	215·6	1·120	∞	3·25	162·9	—
0·75	4·21	211·0	1·116			Mean	1·11

(*b*) p-*Toluidide.* Strength of solution, 0·9872 g./100 c.c. (0·030 g.-mol./l.). $[\alpha]_0 = 249°$. $[\alpha]_\infty = 153°$.

Mean value of *k* (9 observations) = 1·21 hr.$^{-1}$ (max., 1·23; min., 1·17).

(*c*) p-*Bromoanilide.* Strength of solution, 1·000 g./100 c.c. (0·026 g.-mol./l.). $[\alpha]_0 = 239°$. $[\alpha]_\infty = 139°$.

Mean value of *k* (11 observations) = 1·20 hr.$^{-1}$ (max., 1·26; min., 1·15).

(*d*) p-*Chloroanilide.* Strength of solution, 1·000 g./100 c.c. (0·029 g.-mol./l.). $[\alpha]_0 = 266°$. $[\alpha]_\infty = 155°$.

Mean value of *k* (10 observations) = 1·32 hr.$^{-1}$ (max., 1·37; min., 1·29).

(*e*) p-*Anisidide.* Strength of solution, 0·9912 g./100 c.c. (0·029 g.-mol./l.). $[\alpha]_0 = 259°$. $[\alpha]_\infty = 157°$.

Mean value of *k* (9 observations) = 2·37 hr.$^{-1}$ (max., 2·44; min., 2·29).

This series was repeated in the same solvent after it had remained in the thermostat at 25° for a fortnight. The same *order* of velocities was found, although, probably owing to the slight decrease in the concentration of sodium ethoxide present, the *absolute* values of the velocity coefficients were about 20—30% lower in each case.

(*a*) *Anilide.* Strength of solution, 0·7832 g./100 c.c. (0·025 g.-mol./l.). $[\alpha]_0 = 272°$. $[\alpha]_\infty = 163°$.

Mean value of k (9 observations) = 0·73 hr.$^{-1}$ (max., 0·76; min., 0·71).

(*b*) p-*Toluidide.* Strength of solution, 0·8248 g./100 c.c. (0·025 g.-mol./l.). $[\alpha]_0 = 247°$. $[\alpha]_\infty = 153°$.

Mean value of k (9 observations) = 0·98 hr.$^{-1}$ (max., 1·05; min., 0·93).

(*c*) p-*Bromoanilide.* Strength of solution, 0·9809 g./100 c.c. (0·025 g.-mol./l.). $[\alpha]_0 = 241°$. $[\alpha]_\infty = 139°$.

Mean value of k (10 observations) = 0·80 hr.$^{-1}$ (max., 0·83; min., 0·77).

(*d*) p-*Chloroanilide.* Strength of solution, 0·8704 g./100 c.c. (0·025N). $[\alpha]_0 = 267°$. $[\alpha]_\infty = 154°$.

Mean value of k (11 observations) = 1·00 hr.$^{-1}$ (max., 1·04; min., 0·95).

(*e*) p-*Anisidide.* Strength of solution, 0·8704 g./100 c.c. (0·025N). $[\alpha]_0 = 251°$. $[\alpha]_\infty = 152°$.

Mean value of k (9 observations) = 2·14 hr.$^{-1}$ (max., 2·31; min., 2·02).

Series III and IV. Velocity of mutarotation of tetramethyl glucose anilides in 0·001N-*sodium ethoxide in ether at* 25°. In the first and preliminary of these two series an approximately 0·001N-solution of sodium ethoxide in ether was employed, but a very small (constant) quantity of water was present. The alcohol and ether were both dried over sodium, but the rigid precautions to exclude water taken in the next series were omitted. The results obtained are summarised below.

p-Substituent.	Strength of soln. (g./100 c.c.).	$[\alpha]_0$.	$[\alpha]_\infty$.	Mean value of k * (hr.$^{-1}$) (natural logs).
Br	0·9880	250°	137°	3·5
H	0·9904	296	164	3·5
Me	1·0016	254	161	2·3
OMe	1·0016	257	155	6·4

* Obtained graphically from the straight line obtained by plotting t against $\log([\alpha]_0 - [\alpha]_\infty)$.

In the next series, the alcohol used was refluxed over metallic calcium until a large amount of calcium ethoxide was formed; it was then transferred to a dry distillation apparatus closed with drying-tubes containing phosphoric oxide, and, after 12 hours, distilled directly into a dried burette closed with a drying-tube containing phosphoric oxide. The sample so obtained had $d_{4^\circ}^{18^\circ}$ 0·7909, the value for 100% alcohol given in Landolt-Börnstein's tables being 0·79074 at 18°. The sample therefore contained less than 0·1% of water.

The 0·1*N*-sodium ethoxide solution was prepared by the addition of the calculated quantity of clean dry sodium to the known volume of alcohol in the burette, and 2·5 c.c. of this solution were run directly (avoiding long contact with the air) into about 245 c.c. of ether which had been dried and distilled over sodium. The solution was made up to 250 c.c. with a few c.c. of the sample of anhydrous alcohol obtained above, and was left tightly stoppered in a thermostat at 25° overnight before the first set of velocity measurements was taken.

(*a*) p-*Toluidide.* Strength of solution, 0·8256 g./100 c.c. (0·025 g.-mol./l.).

$$[\alpha]_0 = 261^\circ. \quad [\alpha]_\infty = 158^\circ. \quad k = \frac{2{\cdot}3}{t}\log\frac{[\alpha]_\infty - [\alpha]_0}{[\alpha]_\infty - [\alpha]_t}(\text{hr.}^{-1}).$$

t (hrs.).	a.	$[\alpha]_{5461}$.	k.
0·084	3·64°	220·5°	(5·78)
0·117	3·46	209·5	(5·80)
0·15	3·26	197·4	6·27
0·167	3·21	194·4	6·12
0·2	3·10	187·8	6·08
0·22	3·04	184·1	6·23
0·25	2·97	179·9	6·07
0·28	2·90°	175·6°	5·95
0·33	2·83	171·4	5·99
0·5	2·69	162·9	6·28
0·58	2·65	160·4	6·11
1·25	2·60	157·5	—
5·7 (∞)	2·60	157·5	—
		Mean	6·12

(*b*) *Anilide.* Strength of solution, 0·7896 g./100 c.c. (0·025 g.-mol./l.). $[\alpha]_0 = 290^\circ$. $[\alpha]_\infty = 160^\circ$.

Mean value of k (6 observations) = 7·73 hr.$^{-1}$ (max., 7·79; min., 7·63).

(*c*) p-*Bromoanilide.* Strength of solution, 0·9712 g./100 c.c. (0·025 g.-mol./l.). $[\alpha]_0 = 259^\circ$. $[\alpha]_\infty = 142^\circ$.

Mean value of k (7 observations) = 9·14 hr.$^{-1}$ (max., 9·69; min., 8·70).

(*d*) p-*Chloroanilide.* Strength of solution, 0·8752 g./100 c.c. (0·025 g.-mol./l.). $[\alpha]_0 = 270^\circ$. $[\alpha]_\infty = 146^\circ$.

Mean value of k (7 observations) = 11·4 hr.$^{-1}$ (max., 12·3; min., 10·5).

(*e*) p-*Anisidide.* Strength of solution, 0·8744 g./100 c.c. (0·025 g.-mol./l.). $[\alpha]_0 = 257^\circ$. $[\alpha]_\infty = 145^\circ$.

Mean value of k (6 observations) = 14·7 hr.$^{-1}$ (max., 15·5; min., 14·0).

Values of $[\alpha]_\infty$ *in Alkaline and Acid Catalysis Experiments.*—It will be noticed that the end values obtained in the alkaline catalysis experiments agree amongst themselves, but are very different from those obtained in acid catalysis. This was shown to be due entirely to the difference in solvents used—ether in the alkaline catalysis and ethyl acetate in the acid catalysis. The final, constant, value of a solution of tetramethyl glucose *p*-toluidide (0·8416 g.) in 100 c.c. of a 0·9N-solution of acetic acid in ether was $\alpha = 2{\cdot}60^\circ$, whence $[\alpha]_{5461} = 155^\circ$, in good agreement with the end values obtained for this derivative in the alkaline catalysis experiments, and differing from the value (110°) obtained in a 0·9N-solution of acetic acid in ethyl acetate.

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