

each case a preliminary diffusion period of 5 to 10 hours preceded introduction of a fresh solution in compartment B for a diffusion experiment. The initial concentration c_0 in compartment A was 5×10^{-4} molar.

To determine the cell constant for work with ethanol solutions 2×10^{-4} M maleic acid was examined at pK 1 (0.05 M perchloric acid). The wave height obtained indicated a diffusion current of 1.10 microamperes and a two-

electron reduction; it was approximately one-half the wave obtained under like conditions for *m*-nitroacetanilide. Calculation of D for *m*-nitroacetanilide from the Ilkovic equation⁶ with $n = 4$ yields the result 0.66×10^{-5} cm.² sec.⁻¹ at pK 8. From the value of KD for *m*-nitroacetanilide at 24° the cell constant was calculated to be $K = 0.50$.

PHILADELPHIA, PENNSYLVANIA RECEIVED OCTOBER 8, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Concerted Displacement Reactions. VII. The Mechanism of Acid-Base Catalysis in Non-aqueous Solvents¹

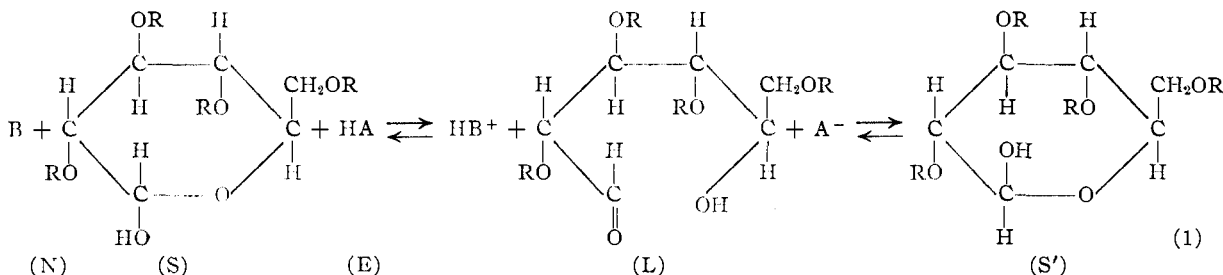
BY C. GARDNER SWAIN AND JOHN F. BROWN, JR.

The mutarotation of α -D-tetramethylglucose (S) catalyzed by phenol-pyridine or other acid (E)-base (N) mixtures in benzene solution is first order in N, first order in S, and first order in E, hence third order over-all. This kinetics requires what we previously defined as a "concerted" mechanism. This involves no intermediate in which the sugar has either gained or lost a proton. A proton must be gained from the acid (E) only in the same step that proton transfer to the base (N) occurs, and this gives the aldehyde (L) directly.

The mutarotation of sugars is a convenient model reaction for studies of homogeneous catalysis. Previous studies have demonstrated that the rate-determining step is the formation of the free aldehyde (L), which then rapidly cyclizes^{2,3}; that catalysis is general with respect to both acids and bases^{4,5}; and that both a base (B) and an acid (HA) must be present in order for the reaction to proceed.^{5,6}

acid and the base (two separate molecules) upon the sugar to give L directly; the other, first stated in its present form by Pedersen,⁸ holds that the proton transfers occur *successively*, so that either the conjugate acid (cation) or the conjugate base (anion) of the sugar (S) is an intermediate in the conversion $S \rightarrow L$.

Our recent independent measurements of the complexing of pyridine and phenol in benzene solu-



Equation 1 represents the mutarotation of α -D-glucose or α -D-tetramethylglucose (S) to the β -D-isomer (S'). We choose the symbols N, S and E because the base is a nucleophilic reagent, the compound undergoing displacement is the substrate, and the acid is an electrophilic reagent. The open-chain aldehyde intermediate is much less stable than S or S', and rapidly cyclizes partly back to S and partly to S'. Hence, the rate constant measured experimentally is proportional to the rate constant for the rate-determining step $S \rightarrow L$.

There are, however, two different viewpoints as to the manner in which the proton transfers occur. One^{6,7} holds that there is a *concerted* attack of the

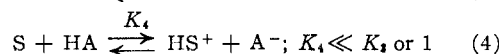
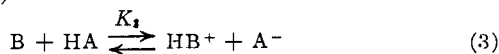
tion⁹ permit us to correct for the association and complexing phenomena involved when pyridine and phenol are used as catalysts for the mutarotation of tetramethylglucose, and to distinguish between these two viewpoints for the first time.

Results.—The mutarotation of α -D-tetramethylglucose (S) catalyzed by monofunctional acids (E) and monofunctional bases (N) in benzene solution at 25° is third order. The measured rate constant is

$$k_1 = \Sigma k_3 [N] [E] \quad (2)$$

This is the first time that third-order kinetics has been proved for the mutarotation of a sugar in an inert solvent.

If any form of the Pedersen mechanism⁸ were valid, different kinetics would result. Let the conjugate base of L be represented by J^- (let $L = \bar{H}J$).



(8) K. J. Pedersen, *J. Phys. Chem.*, **38**, 581 (1934).

(9) C. G. Swain and John F. Brown, Jr., *THIS JOURNAL*, **74**, in press (1952).

(1) For previous papers see *Record of Chemical Progress*, **12**, 21 (1951); *THIS JOURNAL*, **73**, 2813 (1951). For more complete experimental data related to this paper and Paper VIII, see J. F. Brown, Jr., Ph.D. Thesis, M. I. T., July, 1950.

(2) T. M. Lowry, *J. Chem. Soc.*, **127**, 1383 (1925).

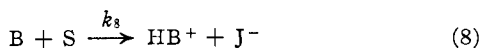
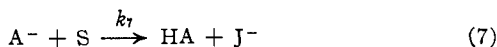
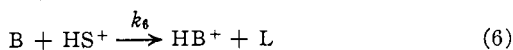
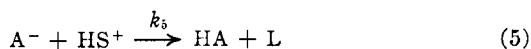
(3) H. Fredenhagen and K. F. Bonhoeffer, *Z. physik. Chem.*, **181**, 392 (1938); K. Goto and T. Titani, *Bull. Chem. Soc. Japan*, **16**, 403 (1941); K. Wiesner, *Coll. Czech. Chem. Comm.*, **12**, 64 (1947).

(4) J. N. Brønsted and E. A. Guggenheim, *THIS JOURNAL*, **49**, 2554 (1927).

(5) T. M. Lowry and G. F. Smith, *J. Chem. Soc.*, 2539 (1927).

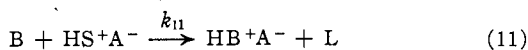
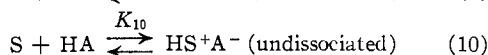
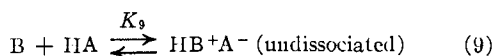
(6) T. M. Lowry and I. J. Faulkner, *ibid.*, **127**, 2883 (1925).

(7) C. G. Swain, *THIS JOURNAL*, **72**, 4578 (1950).

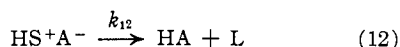


By successively assuming equations 5-8 as principal rate-determining steps, one obtains *only second-order equations*, none of which agrees with the experimental third-order equation 2.

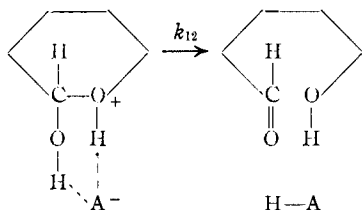
Assuming that part or all of the salts exist as undissociated ion pairs still does not give equation 2. The mechanism



would do so provided

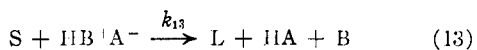


were negligibly slow. However, it is quite unreasonable that the rate of 12 should be slow compared to 11, because A^- (phenoxide ion) is a stronger base than B (pyridine) and is ideally located in space for rapid reaction. Molecular

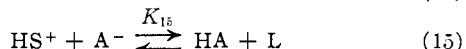
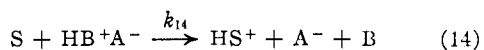


models make this particularly evident. If a high-energy intermediate like HS^+A^- were formed, it should therefore react as in 12 to give a second-order equation.

If all ions were associated and the mechanism involved reaction 9 followed by

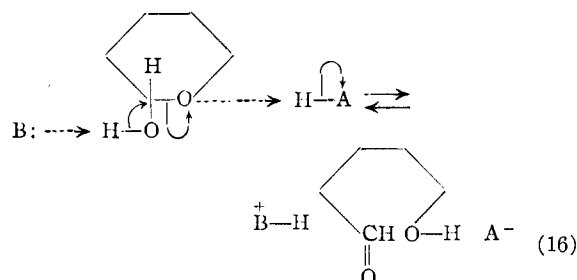


equation 2 would follow. This requires a more detailed consideration of what is meant by equation 13. If 13 is a two-step process



then it is not clear why HA should not be able to donate a proton to S just as effectively as HB^+A^- , which is often in lower concentration than HA. On the other hand, if 13 is a one-step process, then reactions 9 and 13 are not the Pedersen mechanism: they involve the conjugate acid of the catalyzing base and conjugate base of the catalyzing acid, but not the conjugate acid or base of S. It is already certain that there is a mobile acid-base equilibrium between B and HA; hence this last mechanism is physically no different than the concerted mechanism.

Thus the concerted mechanism must be the one which is actually operating. This involves attack upon the sugar molecule by *both* a base and an acid, resulting in the simultaneous¹⁰ addition and removal of protons and rupture of the C-O bond. The fact that this route can lead to L directly without going through any high-energy intermediates such as the conjugate acid (HS^+A^-) or conjugate base of the sugar is no doubt the reason why nature prefers it to one involving *either* B or HA alone.



This proof that the concerted mechanism is correct, *i.e.*, that an acid and a base act *simultaneously* to produce catalysis, leads to a prediction (which could not have been made if the Pedersen theory had been accepted as correct): it should be possible to find a polyfunctional molecule, containing properly oriented acidic and basic parts, which can do the job alone in an inert solvent. Such a "polyfunctional catalyst" has been found and is the subject of the next paper (VIII) in this series.

Comparison with More Polar Solvents.—Third-order kinetics has neither been proved nor disproved for aqueous solutions thus far. Therefore, one cannot also rigorously exclude the Pedersen mechanism for mutarotation in water solution. However, third-order kinetics is consistent with the data for water solutions and has been proved for a very similar reaction, the enolization of acetone in water solution.⁷ Here also, in the region pH 2-7, nature evidently prefers a concerted mechanism in which the substrate (acetone) stays uncharged instead of one proceeding through either the conjugate acid of acetone or the conjugate base (enolate ion).¹²

Comparison with the pyridine-cresol mixtures

(10) It was earlier pointed out¹¹ that there is no physically significant difference between (1) a termolecular reaction and (2) a loose reversible association of two of the reactants in a weak electrostatic or hydrogen-bonded complex followed by slow reaction with the third reactant. We have used the word "concerted" to describe this situation in which three or more reactants must come together before any covalency changes can occur. Similarly in this process, it is regarded as possible, and indeed very likely, that the sugar may form hydrogen bonds to a greater or lesser extent with either the acid or base or both preliminary to the main reaction. However, the actual proton transfers occur simultaneously; *i.e.*, the conjugate acid or base of the sugar is not an intermediate.

(11) C. G. Swain, *THIS JOURNAL*, **70**, 1125 (1948); C. G. Swain and R. W. Eddy, *ibid.*, **70**, 2992 (1948).

(12) However, simply because ionic conjugate acid or conjugate base intermediates are not involved in reactions catalyzed by weak acids or bases such as phenol or pyridine, *i.e.*, with the reagents and conditions commonly used for demonstrating "general acid" or "general base" catalysis, one cannot say that they never occur. They probably *are* involved under other conditions, *viz.*, in strongly acidic (glucose in aqueous sulfuric acid) or strongly basic (aqueous sodium hydroxide) media.

(with no inert solvent) used by Lowry and Faulkner⁶ shows that in spite of the fact that their solvent was more polar than ours and not constant from one experiment to the next (preventing the rigorous demonstration of third-order kinetics), there actually was surprisingly little effect of the solvent on the mechanism. Their results suggest the same kinetic dependence on pyridine and phenol, and their rates even agree semi-quantitatively with ours without any correction for medium change (see experimental section).

Experimental

Materials Used.—The benzene was Mallinckrodt analytical reagent grade, dried over sodium wire.

Tetramethylglucose was prepared by the "Organic Syntheses" procedure.¹³ Three different samples were used, which apparently differed slightly in their ratios of α - to β -forms, since they differed in their physical properties, but not in their mutarotation behavior. The samples had specific rotations ($[\alpha]^{25}_D$) of $112 \rightarrow 91^\circ$, $118 \rightarrow 90^\circ$, and $118 \rightarrow 90^\circ$ (2% solution in benzene); and melting points (cor.) of $85\text{--}93^\circ$, $95\text{--}99^\circ$ and $91\text{--}96^\circ$, respectively.

Mallinckrodt analytical reagent phenol and pyridine were dried over Drierite. The *p*-nitrophenol, 2,4-dinitrophenol and picric acid were Eastman Kodak Co. pure chemicals, recrystallized twice with the aid of Florex (Florida clay) from benzene.

Kinetic Method.—The kinetics with both phenol and pyridine present was actually third order (equation 2). However, since both phenol and pyridine were catalysts and neither was consumed, any given run by itself was first order. The first-order rate constants, k_1 , were determined from the optical rotations by the relationship

$$k_1 = \frac{2.303}{t} \log \frac{\alpha_0 - \alpha_\infty}{\alpha_t - \alpha_\infty} \quad (17)$$

where α_t = observed rotation at time t , $\alpha_0 = \alpha_t$ at $t = 0$, $\alpha_\infty = \alpha_t$ at equilibrium.

Mutarotations were run in a semi-micro 20-cm. water-jacketed polarimeter tube, held at $25.00 \pm 0.01^\circ$ by water circulated from a thermostat. In making a run, 3 ml. of a benzene solution of the catalyst was added rapidly from a calibrated pipet to a weighed portion of tetramethylglucose, which dissolved instantly. The solution was transferred as rapidly as possible to the polarimeter tube, and readings commenced.

The precision of the k_1 values was about $\pm 4\%$ in the early runs (up to run 15) but gradually increased to about $\pm 1\text{--}2\%$ in the later runs. No departure from first-order kinetics was observed and the final specific rotation of the solutions was always the same as that in runs using only pure tetramethylglucose.

Mutarotation in Pure Benzene.—Paralleling the experience of Lowry and Richards,¹⁴ a slow mutarotation was observed when tetramethylglucose was dissolved in benzene in the absence of any added catalyst. The rate of this uncatalyzed "blank" was smaller than that observed by Lowry and Richards, and moreover tended to drop during the course of the work. On various occasions, values of 1.3, 2.0, 1.4, and 0.23×10^{-6} sec.⁻¹ were observed for 0.09 *M* solutions of tetramethylglucose, and 0.62×10^{-6} sec.⁻¹ for a 0.18 *M* solution. In view of the small and variable nature of this blank, it was assumed to be due to the catalytic action of traces of impurities in the solutions. In most of the following work, this blank was assumed to have the value 1.3×10^{-6} sec.⁻¹.

Catalysis by Phenol.—Acceleration of the rate of mutarotation upon the addition of phenol was observed, but again the results were of a highly erratic nature, particularly in giving stray points in which there was almost no catalysis. The action of accidental impurities, in conjunction with phenol or phenol polymers was suspected. The kinetics of the catalysis could be approximated by the equation

$$k_1 = 0.0000013 + 0.0081[\text{C}_6\text{H}_5\text{OH}]^2 \text{ sec.}^{-3} \quad (18)$$

(13) E. S. West and R. F. Holden, *Org. Syntheses*, **20**, 97 (1940).

(14) T. M. Lowry and E. M. Richards, *J. Chem. Soc.*, **127**, 1385 (1925).

where $[\text{C}_6\text{H}_5\text{OH}]$ is the concentration of free phenol monomer, a quantity slightly smaller than the total phenol concentration. For example, k_1 for 0.100 *M* total phenol (0.091 *M* free phenol) and 0.09 *M* tetramethylglucose in run 17 was 7.0×10^{-6} sec.⁻¹ observed, 7.3×10^{-6} sec.⁻¹ calculated. Equation 18 was not regarded as having any mechanistic significance, but only as a means of obtaining phenol "blanks," or corrections to be applied for catalysis by phenol alone in analyzing the catalytic effects of mixtures of phenol and bases. Fortunately, these corrections were always very small, so that their uncertainties did not significantly affect any of the conclusions derived.

Catalysis by Pyridine.—The catalytic effect of pyridine was found to be dependent upon the tetramethylglucose concentration ($R = S + S'$). The kinetics could be expressed by the equation

$$k_1 = 0.0000013 + 0.00048[\text{C}_5\text{H}_5\text{N}][R] \text{ sec.}^{-1} \quad (19)$$

The data and the agreement with equation 19 are given in Table I.

TABLE I
CATALYSIS OF THE MUTAROTATION OF TETRAMETHYL-
GLUCOSE BY PYRIDINE IN BENZENE AT 25°

Run no.	R, M	Pyridine, M	$k_1 \times 10^6$, sec. ⁻¹ Calcd.	Found
54	0.093	0.049	3.5	3.5
16	.093	.100	5.8	6.1
70	.182	.096	9.0 ^a	8.5

^a For this run, the uncatalyzed rate was assumed to be 0.6×10^{-6} rather than 1.3×10^{-6} sec.⁻¹ on the basis of a blank taken on a 0.18 *M* tetramethylglucose solution just before the run.

Catalysis by Pyridine-Phenol Mixtures.—Including the terms already found to represent the blank, and catalysis by phenol and pyridine separately, the kinetics of mutarotation catalyzed by pyridine-phenol mixtures may be expressed as

$$k_1 = 0.0000013 + 0.0081[\text{C}_6\text{H}_5\text{OH}]^2 + 0.00048[\text{C}_5\text{H}_5\text{N}][R] + 0.021[\text{C}_5\text{H}_5\text{N}][\text{C}_6\text{H}_5\text{OH}] + 0.84[\text{C}_5\text{H}_5\text{N}][\text{C}_6\text{H}_5\text{OH}]^2 \text{ sec.}^{-1} \quad (20)$$

where $[\text{C}_5\text{H}_5\text{N}]$ and $[\text{C}_6\text{H}_5\text{OH}]$ are the concentrations of the free, uncomplexed and unassociated pyridine and phenol⁶ (see Table II). The last term, which is important only at high phenol concentrations, may be due to the action of either pyridine and a phenol dimer, or a pyridine-phenol complex and phenol, or a combination of these. Thus, except for the very small blank due to unknown impurities, no term is less than third order, even in very dilute solution.

TABLE II
CATALYSIS OF THE MUTAROTATION OF 0.09 *M* TETRAMETHYL-
GLUCOSE BY PYRIDINE AND PHENOL IN BENZENE AT 25°

Run no.	Total pyridine, M	Total phenol, M	Free pyridine, M	Free phenol, M	$k_1 \times 10^6$, sec. ⁻¹ Calcd.	Found
14	0.020	0.100	0.0068	0.076	47	43
12	.050	.100	.020	.059	88	90
11	.100	.100	.052	.041	121	131
15	.100	.050	.072	.019	55	58
34	.098	.0245	.085	.0090	27	25
33	.049	.049	.031	.0275	40	40

Equation 20 for dilute benzene solutions is surprisingly consistent with the older data of Lowry and Faulkner⁶ on mutarotation in pure pyridine-cresol mixtures (no inert solvent). In a pure pyridine-phenol equimolar mixture, the calculated rate (using 1.64 *M* free pyridine and 0.093 *M* free phenol, calculated from equilibrium constants determined in dilute benzene solution) is 0.015 sec.⁻¹ at 25° . This may be extrapolated to 0.01 sec.⁻¹ at 20° . Lowry and Faulkner found 0.004 sec.⁻¹ for an equimolar pyridine-*o*-cresol mixture at 20° .

Catalysis by Nitrophenols.—The data were insufficient to demonstrate the kinetic order of the catalysis, but did show the necessity of having both an acid and a base in order

to have rapid catalysis (see Table III). The lower catalytic power of 2,4-dinitrophenol paralleled its lower ability to complex with pyridine.⁹

TABLE III

CATALYSIS OF THE MUTAROTATION OF 0.09 *M* TETRAMETHYLGLUCOSE BY NITROPHENOLS IN BENZENE AT 25°

Run no.	Phenol	Total phenol, <i>M</i>	Total pyridine, <i>M</i>	$k_1 \times 10^6$, sec. ^{-1a}
51	<i>p</i> -Nitrophenol	0.049	...	0.2
56	<i>p</i> -Nitrophenol	.047	0.049	315
59	2,4-Dinitrophenol	.050	...	1.9
58	2,4-Dinitrophenol	.050	.049	112

^a Corrected for solvent blank.

Catalysis by 3-Hydroxyquinoline.—The catalysis of the reaction by 3-hydroxyquinoline was studied in acetone rather than in benzene solution because of the extremely low solubility of the compound in the latter solvent. The rate of mutarotation was

$$k_1 = 0.00027[3\text{-HOC}_6\text{H}_5\text{N}]^2 \quad (21)$$

No mutarotation could be detected in acetone solution in the absence of catalysts.

Comparison of Catalysts.—The results show that the catalysis of the mutarotation of tetramethylglucose in inert solvents by various simple acids (E) and bases (N) may be represented by equation 2. Apparently, tetramethylglucose itself can act as an acid, but not as a base. Table IV gives the k_3 values for the various acid-base pairs already discussed, as well as giving approximate values of k_3 for other systems where both an acid and a base were found necessary, but where only fragmentary studies were made. Each term in the expression for k_1 was divided by $[N][E]$ to obtain k_3 .

The fact that 2,4-dinitrophenol is a less effective catalyst than *p*-nitrophenol may be due to steric hindrance of the *o*-nitro-substituent. This is indicated also by the lower ability of 2,4-dinitrophenol to complex with pyridine.⁹

The $[\text{C}_6\text{H}_5\text{N}][\text{C}_6\text{H}_5\text{OH}]^2$ term found in catalysis by phenol-pyridine mixtures cannot be unambiguously assigned a k_3 value. The term might arise from the action of either a $\text{C}_6\text{H}_5\text{N}-(\text{C}_6\text{H}_5\text{OH})_2$ pair ($k_3 = 1.47 \text{ M}^{-2} \text{ sec.}^{-1}$) or a $(\text{C}_6\text{H}_5\text{N}-\text{C}_6\text{H}_5\text{OH})-\text{C}_6\text{H}_5\text{OH}$ pair ($k_3 = 0.046 \text{ M}^{-2} \text{ sec.}^{-1}$) or more likely some combination of the two, each with a correspondingly lower k_3 value.

A typical kinetic run is presented in Table V.

TABLE IV

MUTAROTATION OF TETRAMETHYLGLUCOSE IN BENZENE SOLUTION AT 25°

Base	Acid	k_3 , $\text{M}^{-2} \text{ sec.}^{-1}$
3-Hydroxyquinoline	3-Hydroxyquinoline	0.00027 ^a
2-Methoxypyridine	Phenol	.001 ^{b,c,d}
N-Methyl- α -pyridone	Phenol	.01 ^{b,c,d}
Pyridine	Tetramethylglucose	.0005
Pyridine	Phenol	.021
Pyridine	<i>p</i> -Nitrophenol	1.1 ^b
Pyridine	2,4-Dinitrophenol	0.05 ^b
4-Aminopyridine	Tetramethylglucose	.27 ^b
Triethylamine	Tetramethylglucose	.04 ^b
Hydroxide ion	Water	4. ^e
Pyridine	Water	0.0001 ^e
Water	Water	.0000001 ^e
Water	Hydronium ion	.0002 ^e

^a This refers to an acetone rather than a benzene solution. ^b These values are based on limited data. ^c These values represent only estimated orders of magnitude, since data on the acid-base complexing were not available. ^d See following Paper VIII. ^e This refers to a water (55 *M*) rather than a benzene solution. Data from G. F. Smith and M. C. Smith, *J. Chem. Soc.*, 1413 (1937), and reference 4.

TABLE V

RUN 12. MUTAROTATION OF 0.0922 *M* TETRAMETHYLGLUCOSE WITH 0.10 *M* PHENOL AND 0.050 *M* PYRIDINE IN BENZENE AT 25°

Time, min.	Rotation, deg.	$k_1 \times 10^6$, sec. ⁻¹
0	4.90	..
24	4.79	90.
53	4.67	92.
75	4.59	92.
98	4.54	85.
126	4.44	93.
167	4.36	89.
192	4.32	87.
222	4.265	88.
1200	3.98	..

Average $90 \pm 2 \times 10^{-6} \text{ sec.}^{-1}$

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