

A Kinetic Study of Michaelis-Arbuzov Reactions

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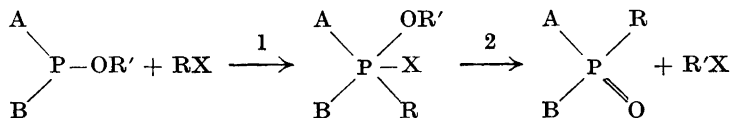
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The reactions of ethyl iodide with triethyl phosphite, diethyl benzenephosphonite, ethyl dibenzenephosphinite, and triphenyl phosphine have been studied, in acetonitrile as well as in the absence of added solvent. The phosphite, phosphonite and phosphinite give normal Michaelis-Arbuzov products: diethyl ethanephosphonate, ethyl ethane-benzenephosphonate, and ethyl diphenyl phosphine oxide. Their rates of formation in acetonitrile obey first order kinetics and are directly proportional to the ethyl iodide concentration. The concentration of ethyl iodide remains effectively constant during the rearrangement. It is concluded that formation of a phosphonium intermediate is the rate determining step of the reaction. The reaction of triphenyl phosphine with ethyl iodide shows second order kinetics in accordance with the formation of a stable phosphonium salt.

The sigmoid shaped concentration-time curve observed for the Michaelis-Arbuzov rearrangements in the absence of added solvent is assumed to be due to a change of dielectric constant of the reaction solution during the rearrangement.

The activation energies and entropies of the various reactions are discussed.

The Michaelis-Arbuzov reaction between alkyl halogenides and triply linked phosphorus compounds containing at least one alkoxy group directly linked to phosphorus has been extensively studied with respect to its utilization for the synthesis of esters of primary and secondary phosphonic acids as well as phosphine oxides.¹ Arbuzov² proposed a two-step mechanism, with the formation of an intermediate pentacovalent phosphorus compound in the first step:



A and B are alkyl, alkoxy, dialkylamino *etc.*, and R' and R are alkyl groups. Evidence for the presence of a pentacovalent intermediate in alkyl halogenide-phosphite reaction mixtures was supposedly obtained from measurements of

viscosity and conductivity of the mixtures.³ Kosolapoff⁴ measured the rate of formation of alkyl halogenide during Michaelis-Arbuzov reactions and showed that the concentration-time curve for the production of halogenide was sigmoid. The results were taken as an indication of the presence of considerable amounts of a phosphonium intermediate. Aromatic phosphites have long been known to form stable phosphonium compounds with alkyl halogenides.⁵ The postulate that the Michaelis-Arbuzov reaction of alkoxy substituted phosphites passes over an intermediate compound seems therefore to be well founded. The character (covalent or ionic) of this intermediate under different conditions and the amount in which it is present during the reaction has however been disputed.³⁻⁸ Gerrard and Green⁷ observed that the Michaelis-Arbuzov reaction of optically active tri-2-octyl phosphite made from (+)-octan-2-ol and ethyl iodide gave (-)-2-iodooctane. The observed inversion was assumed to be due to a S_N2 displacement by iodide ion on the alkoxy carbon in the phosphonium cation.

Buck and Yoke⁹ reported that the second step appeared to be rate determining in the Michaelis-Arbuzov reaction between ethyl iodide and tributyl phosphite in acetonitrile. In a recent study¹⁰ the present authors could not confirm this finding. It was shown that almost no reaction took place between ethyl iodide and tributyl phosphite under the conditions specified by Buck and Yoke, when the acetonitrile was dried over phosphorus pentoxide. However, very small amounts of water in the acetonitrile caused a rapid splitting of tributyl phosphite to dibutyl hydrogen phosphite. The observations of Buck and Yoke⁹ are therefore believed to be due to an incomplete removal of water from the acetonitrile. In the same note¹⁰ we reported that the first step appeared to be rate determining in the Michaelis-Arbuzov rearrangement of triethyl phosphite with ethyl iodide in acetonitrile. In this paper a full account of the work is given together with studies of corresponding reactions of other trivalent phosphorus compounds.

EXPERIMENTAL

Triethyl phosphite made from phosphorus trichloride and absolute ethanol in presence of dimethyl aniline, was thoroughly freed from diethyl hydrogen phosphite by treatment with sodium wires in dry ether. After several fractionations a pure product was obtained, b_s 42.5°, n_D^{20} 1.4125 (Lit.¹ b_{12} 48.2°, n_D^{20} 1.41209).

Diethyl ethanephosphonate was made by boiling a mixture of 20 g triethyl phosphite and 20 g ethyl iodide for one hour. Distillation gave 17 g product, b_s 82°, n_D^{20} 1.4162 (Lit.¹ b_{12} 85°, n_D^{20} 1.4163).

Diethyl benzenephosphonite was synthesized by adding 25 g phenyl dichlorophosphine diluted with 100 ml dry ether to a mixture of 12.7 g absolute ethanol and 33.4 g dimethyl aniline in 300 ml absolute ether. Dimethyl aniline hydrochloride was filtered off and the solvent mixture distilled. After two fractionations a pure product was obtained, b_s 106–107°, n_D^{22} 1.5120 (Lit.¹¹ b_s 100°, n_D^{19} 1.5130).

Ethyl ethane-benzenephosphonate. 20 g diethyl benzene phosphonite was boiled for one hour with 20 g ethyl iodide. Distillation gave 16 g product, b_s 144°, n_D^{21} 1.5128 (Lit.¹ 162–164°).

Ethyl dibenzenephosphinite. 16.7 g of diphenyl chlorophosphine dissolved in 50 ml dry ether was added under nitrogen to a solution of 4.2 g absolute ethanol and 10 g dimethyl aniline in 70 ml dry benzene. After filtration of the hydrochloride the product was distilled twice *in vacuo*, $b_{1.0}$ 124–125°, $n_D^{20.6}$ 1.5910 (Lit.¹² b_1 127–128° n_D^{20} 1.5910).

Diphenyl ethyl phosphine oxide was made by boiling triphenyl ethyl phosphonium bromide with an equivalent amount of sodium hydroxide in alcohol. The phosphine oxide was recrystallized twice from benzene, m.p. 124°C. (Lit.¹ 121°).

Triphenyl phosphine. A product from L. Light & Co. was recrystallized twice from ether, m.p. 80°.

Ethyl iodide (E. Merck) was treated with silver powder and distilled, b_{760} 72°.

Acetonitrile (Fluka *puriss.*) was boiled with phosphorus pentoxide for one hour. The fraction boiling between 81–82° was used.

Kinetic measurements. The Michaelis-Arbuzov reaction was followed by measuring the infrared absorption of reactants and products in acetonitrile. The phosphoryl compounds produced during the reaction have all strong P=O bands in the region 1180–1250 cm^{-1} , whereas ethyl iodide has an absorption band at 1204 cm^{-1} . Since trivalent phosphorus compounds usually absorb very weakly in the infrared region used in the present study (1180–1250 cm^{-1}), the change of the concentration of reactant during the reaction had very small influence on the P=O bond absorption. In Fig. 1 are shown the infrared absorption bands used for the quantitative measurements. The variation of the optical density with concentration obeys Beer's law in the concentration range studied. The calibration curves of different bands are plotted in Fig. 2.

Measurements of the optical density of the ethyl iodide band at 1204 cm^{-1} during the different Michaelis-Arbuzov reactions showed that the concentration of ethyl iodide remained constant within experimental error. This reduced the number of variable components in the reaction mixture to two, and the concentration of product (phosphoryl component, $c^{(1)}$) was accordingly obtained from the following equation:

$$E_{\nu_1} = K_{\nu_1}^{(1)} c^{(1)} d + K_{\nu_1}^{(2)} c^{(2)} d$$

where E_{ν_1} = optical density, and $K_{\nu_1}^{(1)}$ and $K_{\nu_1}^{(2)}$ are the molar extinction coefficients of phosphoryl product and trivalent phosphorus reactant, respectively, at the peak wave number of the P=O band and the phosphite band at approximately 1160 cm^{-1} , d = path length of infrared cell and $c^{(1)}$ and $c^{(2)}$ are the concentrations of product and reactant.

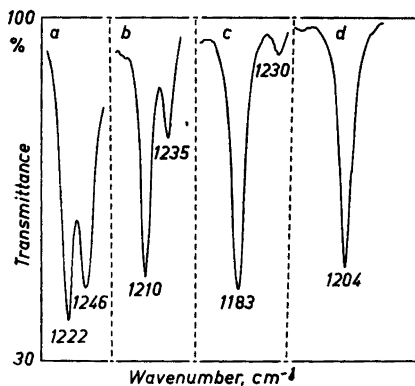


Fig. 1. P=O stretching vibration bands of (a) ethyl ethanephosphonate, (b) ethyl benzene-ethanephosphonate, and (c) ethyl diphenyl phosphine oxide. (d) Infrared absorption band of ethyl iodide.

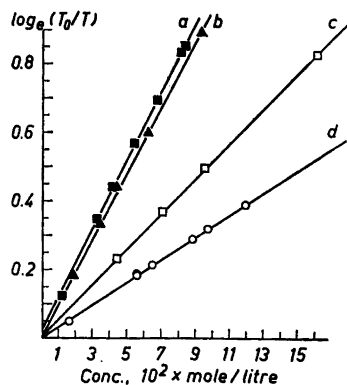


Fig. 2. Linear dependence between optical density of P=O band and concentration of corresponding phosphoryl compound (a) ethyl benzene-ethanephosphonate, (b) ethyl diphenyl phosphine oxide, (c) diethyl ethanephosphonate. (d) Linear dependence between concentration of ethyl iodide and the optical density of its infrared band at 1204 cm^{-1} .

Samples withdrawn from the reaction solution in acetonitrile were cooled to room temperature and immediately transferred to a cell and recorded on a Unicam spectrophotometer, S. P. 100, MK2. For every rate constant calculated, 10–12 separate determinations of concentrations, in the region where 20–70 % of phosphoryl compound had been formed, were performed. The path length of the cells was determined for each separate run using the interference method (cell length approx. 0.1 mm). All values of optical densities were average values of at least two separate recordings of the spectrum. Since the concentration of ethyl iodide was constant during the rearrangement, the spectra were normally compensated against acetonitrile containing the same amount of ethyl iodide as the reaction solution.

The reaction between triphenyl phosphine and ethyl iodide which stops on the phosphonium step, was followed in acetonitrile by measuring the decrease of optical density of the ethyl iodide band at 1204 cm^{-1} (Figs. 1 and 2). Triphenyl phosphine and triphenyl ethyl phosphonium iodide were found to have almost no infrared absorption around 1200 cm^{-1} .

The concentration of phosphoryl product in Michaelis-Arbuzov reaction mixtures in the absence of solvent was determined after dilution with dry benzene. The recorded spectra were compensated against benzene.

RESULTS AND DISCUSSION

The experimental data for the reactions between ethyl iodide and different trivalent phosphorus compounds in acetonitrile are plotted in Figs. 3, 4, 5,

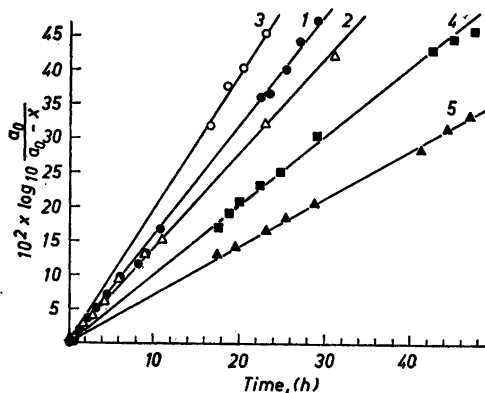


Fig. 3. Pseudo first order plot of the reaction between triethyl phosphite and ethyl iodide. The numbers on the curves refer to the series numbers in Table 1.

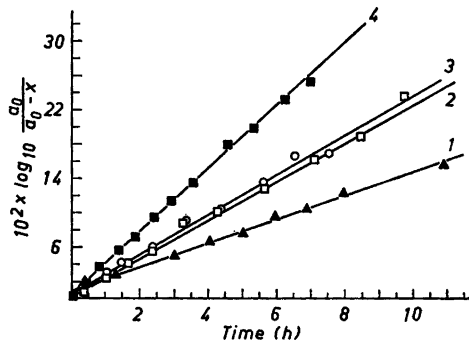


Fig. 4. Pseudo first order plot of the reaction between diethyl benzenephosphonite and ethyl iodide. The numbers on the curves refer to the series numbers in Table 1.

and 6, and the results are summarized in Table 1. In accordance with our previous findings¹⁰ the Michaelis-Arbuzov rearrangement of triethyl phosphite, diethyl benzenephosphonite, and ethyl dibenzenephosphinite with ethyl iodide in acetonitrile follows first order kinetics. The observations that the ethyl iodide concentration remains constant during the reaction and that the rate

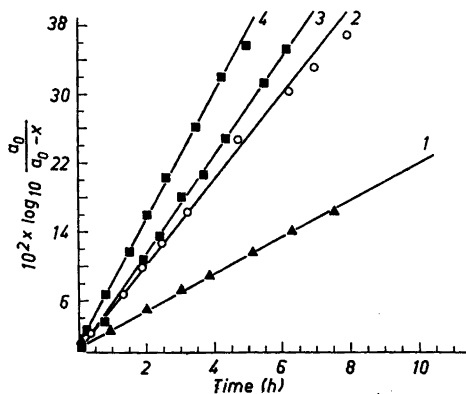


Fig. 5. Pseudo first order plot of the reaction between ethyl dibenzephosphinite and ethyl iodide. The numbers on the curves refer to the series numbers in Table 1.

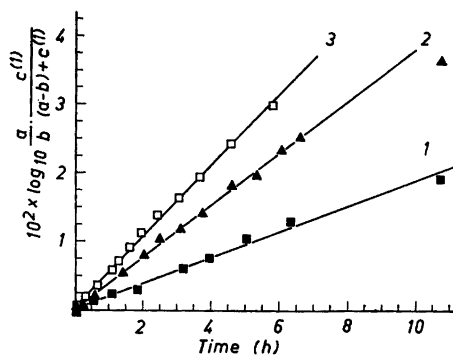
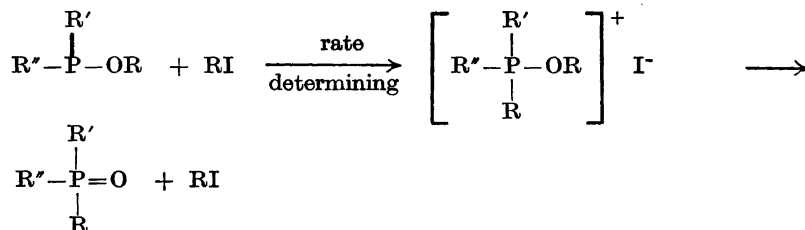


Fig. 6. Second order plot of the reaction between triphenyl phosphine and ethyl iodide. The numbers on the curves refer to the series numbers in Table 1.

of rearrangement is directly proportional to the concentration of ethyl iodide indicate that the first step is rate determining:



The non-influence of added sodium iodide on the rate of reaction also points to the same conclusion (Table 1).

The reaction of triphenyl phosphine and ethyl iodide, where no decomposition of the phosphonium salt can take place, is in accordance with second order kinetics (Fig. 6).¹⁶

Arbuzov and co-workers³ have reported that measurements of viscosity and conductivity of reaction mixtures of triethyl phosphite and ethyl iodide without added solvent indicated the presence of a pentacovalent phosphorus intermediate. We have studied the same reaction in infrared and have not been able to detect any change of ethyl iodide concentration during the rearrangement. The concentration of phosphonium intermediate must therefore be very small. The specific rate at the beginning of the rearrangement was found to be much lower than for the same reaction in acetonitrile. We ascribe the low rate to the much less polar character of the phosphite-ethyl iodide mixture as compared to the acetonitrile solution. The rate determining step, the formation of the phosphonium intermediate, will be much faster in media of high than

Table 1. Rate data for the reaction of trivalent phosphorus compounds with ethyl iodide in acetonitrile.

Compound	Series number	Reaction temp °C.	Start conc. of phosphorus compound, 25.5°C	Start conc. of ethyl iodide, 25.5°C	Start conc. of ethyl iodide at reaction temp.	Conc. of NaI, 25.5°C	Pseudo 1st order rate const. sec ⁻¹ × 10 ⁵	2nd order rate const. l/mole sec × 10 ⁴
(EtO) ₃ P	1	69.90	0.1996	0.2296	0.2131	—	1.03	0.48
	2	69.90	0.1735	0.2110	0.1961	0.01378	0.90	0.46
	3	65.05	0.4409	0.4670	0.4506	—	1.26	0.28
	4	65.05	0.2003	0.2263	0.2133	—	0.65	0.30
	5	60.05	0.2039	0.2329	0.2223	—	0.46	0.20
Ph(EtO) ₂ P	1	44.95	0.1482	0.1640	0.1601	—	0.88	0.55
	2	52.10	0.1591	0.1613	0.1559	—	1.45	0.93
	3	52.10	0.1682	0.1783	0.1725	—	1.52	0.88
	4	60.05	0.1422	0.1388	0.1324	—	2.38	1.79
Ph ₂ (EtO)P	1	45.00	0.1197	0.1665	0.1626	—	1.35	0.83
	2	52.10	0.1126	0.1604	0.1550	—	2.40	1.55
	3	60.05	0.1093	0.1547	0.1476	—	3.67	2.49
	4	60.05	0.1132	0.1549	0.1478	—	3.53	2.39
Ph ₃ P	1	45.30	0.1126	0.1201	0.1173	—	—	1.64
	2	52.05	0.1523	0.1611	0.1558	—	—	2.75
	3	60.50	0.1526	0.1591	0.1519	—	—	5.18

low dielectric constant (*cf.* Menshutkin reaction^{13,14}). In accordance with this view the rate of Michaelis-Arbuzov rearrangements was found to be extremely low in dry benzene which has a dielectric constant of 2.3. For comparison the dielectric constant of acetonitrile is 36. The transformation of trivalent phosphorus compounds to phosphoryl compounds in Michaelis-Arbuzov reactions in the absence of solvent will rise the dielectric constant of the solution during the reaction due to the very high polarity of the phosphoryl group of the product. The increase of dielectric constant of the medium must be expected to produce a corresponding rise of the rate of rearrangement. Actually, the sigmoid shaped concentration-time curve observed for Michaelis-Arbuzov reactions in absence of solvent (Fig. 7) reveals the autocatalytic course of the rearrangement. We assume that similarly sigmoid shaped concentration-time curves observed by Kosolapoff⁴ for the formation of alkyl halogenides during Michaelis-Arbuzov reactions most probably are due to the same medium effect. Likewise, Papov¹⁵ has described a corresponding autocatalytic course of the isomerization of ethyl dichlorothionophosphate to ethyl dichlorothiophosphate. Since the internal transformation from a P=S group to a P=O group greatly rises the polarity of the molecule a similar autocatalytic effect as mentioned above is highly reasonable.

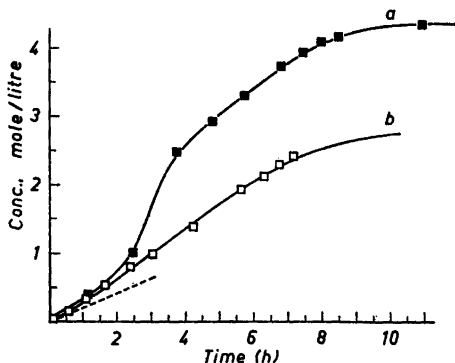


Fig. 7. The rate of formation of ethyl benzene-ethanephosphonate from diethyl benzene-phosphonite and ethyl iodide without added solvent. Start concentrations:

- (a) 4.53 M phosphorus compound and 1.52 M ethyl iodide
 (b) 4.88 M. phosphorus compound and 0.68 M ethyl iodide

Reaction temperature: 59.95°C.

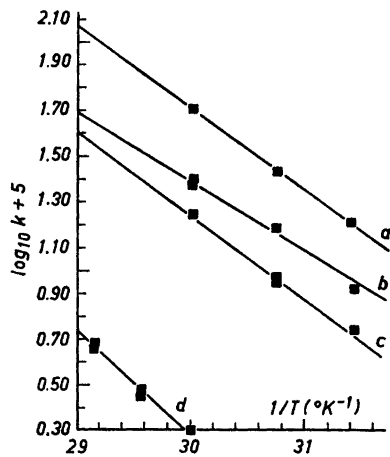


Fig. 8. The Arrhenius activation energy plot, $\log k$ against $1/T$, for the reaction between trivalent phosphorus compounds and ethyl iodide in acetonitrile.

- (a) Ph_3P , (b) $(\text{Ph})_2\text{POEt}$, (c) $\text{PhP}(\text{OEt})_2$,
 (d) $(\text{EtO})_3\text{P}$.

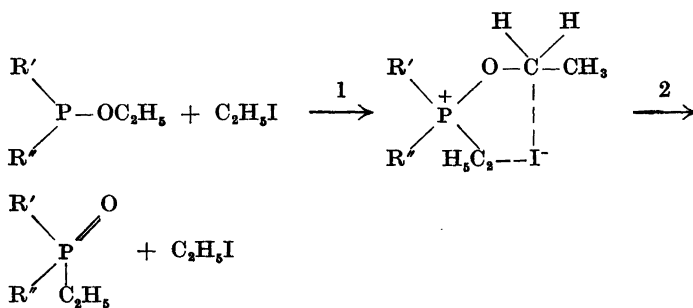
From studies of the temperature dependence of the Michaelis-Arbuzov reactions, the activation energies and entropies have been calculated (Fig. 8 and Table 2). The substitution of a phenyl group for an ethoxy group in the trivalent phosphorus compounds is seen to produce small effect on the rate.

Table 2. Rate constants at 60°C together with thermodynamic data for the reaction between trivalent phosphorus compounds and ethyl iodide in acetonitrile.

Compound	k in l/sec mole at 60°C (extrapolated)	Activation energy E (kcal)	Frequency factor A (l/sec mole)	Activation enthalpy ΔH^* (kcal)	Activation entropy ΔS^* (e.u.)	Free energy of activation ΔF^* at 60°C, (kcal)
$(\text{EtO})_3\text{P}$	0.19	21.0	1.11×10^9	20.3	-19.4	26.8
$\text{Ph}(\text{EtO})_2\text{P}$	1.65	16.9	1.75×10^7	16.2	-27.6	25.4
$\text{Ph}_2(\text{EtO})\text{P}$	2.47	14.0	3.50×10^5	13.3	-35.4	25.1
Ph_3P	4.99	16.0	2.78×10^7	15.3	-26.7	24.2

From the rate data in Table 2, which have been extrapolated to the same temperature (60°C) for all the reactions in Table 1, one might falsely conclude that ethoxy and phenyl groups linked directly to phosphorus produce very similar electronic and steric effects in the molecule. However the activation energies and entropies of the reactions in Table 2 show that the energy required to form the phosphonium intermediate in the reaction of triethyl phosphite with ethyl iodide is 7 kcal higher than in the same reaction of ethyl dibenzene-phosphinite. This effect is probably due to the much stronger $-I$ effect of the ethoxy group as compared with the phenyl group. The same effect is also reflected in the different influence of ethoxy and phenyl groups on the stretching vibration of the P=O group of the products of the Michaelis-Arbuzov reactions. A strong $-I$ effect of the substituents will increase the pd -backbonding from oxygen to phosphorus and will correspondingly rise the vibration frequency of the phosphoryl group (Fig. 1). The increase in activation energy for the phosphonium ion production is nearly compensated by a rise in reaction entropy which causes the rates to remain of comparable magnitude (Table 2). The favourable entropy of activation for the formation of triethoxy ethyl phosphonium iodide from triethyl phosphite and ethyl iodide, as compared to the formation of diphenyl ethoxy ethyl phosphonium iodide, most probably is caused by a greater delocalization of the charge in the former phosphonium compound, due to the strong electrometric effect ($+E$) of the oxygen atoms. This intermediate would require less orientation of solvent molecules and the reaction would therefore have a more favourable entropy of activation.

It is seen from Table 2 that the formation of the stable ethyl triphenyl phosphonium iodide from triphenyl phosphine and ethyl iodide has higher activation energy as well as activation entropy than the Michaelis-Arbuzov rearrangement of ethyl dibenzene-phosphinite. This observation, together with the fact that no phosphonium intermediate has been detected during the Michaelis-Arbuzov reactions studied, may indicate that the second step, the decomposition of the phosphonium intermediate, proceeds before the new valence bonds of the intermediate have been completely developed. The character of the intermediate will thus approach towards the character of a transition state:



A synchronized first and second step will be expected to reduce the activation energy of the rearrangement, whereas the more restricted configuration of such an intermediate correspondingly will lower the activation entropy.

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