α-Bromo Carbonyl Compounds as Promoters for the Synthesis of (2-Bromoethyl)benzene by the Anti-Markovnikov Addition of Hydrogen Bromide to Styrene

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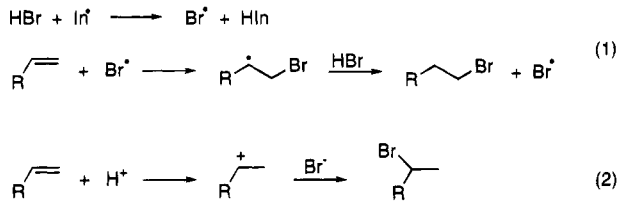
The synthesis of (2-bromoethyl)benzene by the anti-Markovnikov addition of gaseous hydrogen bromide to styrene has been found to be promoted by α-bromo carbonyl compounds such as 2-bromo-2-methylpropanal. These compounds were found to catalyze the "abnormal" addition in a variety of solvents such as ethyl acetate, heptane, toluene and dioxane. High concentrations of 2-bromo-2-methylpropanal and hydrogen bromide and low concentrations of styrene favor formation of (2-bromoethyl)benzene. Using the free-radical catalyzed cyclization of 6-bromo-1-hexene as a probe we have found that the 2-bromo-2-methylpropanal does not in itself initiate a free-radical chain reaction by thermal formation of radicals. Instead, radicals may react with 2-bromo-2-methylpropanal to form relatively stable 2-methylpropanal radicals. The presence of such radicals increases the effective length or inhibits termination of the free-radical chain reaction (propagation) and in the case of hydrobromination of styrene raises the yield of (2-bromoethyl)benzene.

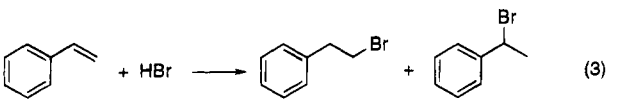
Introduction

Research on the stereochemical orientation of hydrogen bromide addition to alkenes[1] has been more or less dormant for half a century since the finding by Kharasch and co-workers that "abnormal" or anti-Markovnikov addition of hydrogen bromide to alkenes can be elicited by the "peroxide" effect in a radical type mechanism, eq 1, whereas "normal" or Markovnikov addition products are formed by an ionic mechanism via a carbocation intermediate, eq 2.



In general, control of the reaction conditions will allow kinetic control of the reaction pathway so that the desired product can be obtained. Therefore, the anti-Markovnikov addition product can be obtained either by inhibiting the ionic reaction pathway and/or catalyzing the free-radical pathway. Neat reactions or those performed in the presence of polar solvents invariably lead to Markovnikov addition products, whereas addition of peroxides and/or use of apolar solvents (usually aliphatic hydrocarbons) lead to anti-Markovnikov addition products. Addition of hydrogen bromide to styrene, eq 3, to yield exclusively the industrially important (2-bromoethyl)-benzene without coformation of (1-bromoethyl)benzene is notoriously difficult because of the high reaction rates observable for both the free-radical and ionic pathways.

Thus, under the usual best reaction conditions of peroxide (lauryl peroxide) and dilution by an aliphatic



hydrocarbon (pentane) only 80% (2-bromoethyl)benzene can be obtained.[2] Higher (2-bromoethyl)benzene yields have been reported only in the patent literature using initiators including peroxides,[3] AIBN,[4] γ irradiation,[5] and oxygen.[6]

In this paper we report on the use of α-bromo carbonyl compounds in general and more specifically 2-bromo-2-methylpropanal as promoters for the highly selective synthesis of (2-bromoethyl)benzene by the anti-Markovnikov addition of hydrogen bromide to styrene. Additionally, we show that 2-bromo-2-methylpropanal promotes the free radical chain pathway and thus the (2-bromoethyl)benzene yield by sustaining or increasing the amount of free radicals in the reaction mixture without in itself initiating the radical chain reaction.

Results and Discussion

A typical reaction procedure for the addition of hydrogen bromide to styrene was carried out in a batch-type procedure by loading dry hydrogen bromide into a magnetically stirred flask containing styrene, solvent, and α-bromo carbonyl compounds in the dark and at ambient temperature in the presence of atmospheric air. Styrene conversions to the addition products were essentially quantitative. In this research, the molecular oxygen in the reaction mixture served to initiate the radical reaction, eq 4, since reactions performed under conditions where oxygen was removed from the reaction mixture yielded only the Markovnikov addition product, (1-bromoethyl)benzene.

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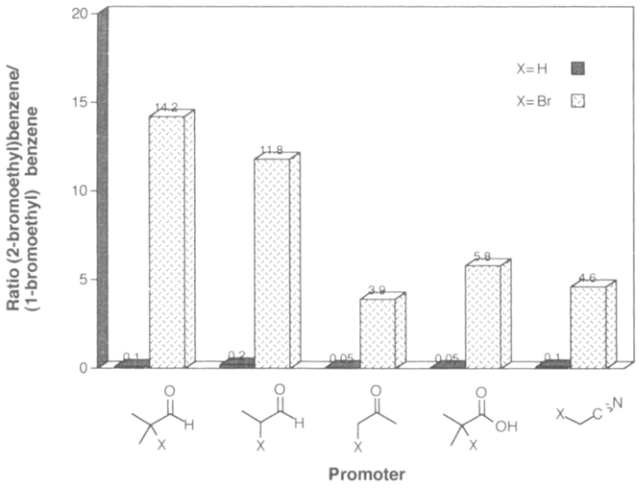

Figure 1. The ratio of (2-bromoethyl)benzene to (1-bromoethyl)benzene in the presence of various promoters. Reaction conditions: 0.0425 mol of promoter, 0.04 mol of HBr, and 0.01 mol of styrene are reacted in 40 mL of ethyl acetate in the dark at 1 atm of air and at 23 °C for 30 min.

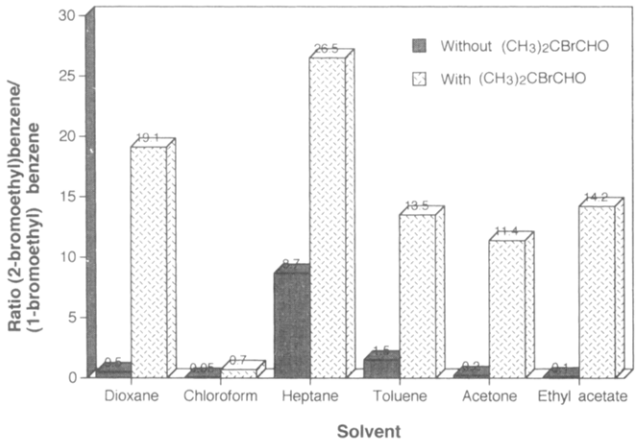

Figure 2. The ratio of (2-bromoethyl)benzene to (1-bromoethyl)benzene as a function of the reaction solvent. Reaction conditions: 0.04 mol of 2-bromo-2-methylpropanal, 0.015 mol of HBr, and 0.01 mol of styrene are reacted in 40 mL solvent in the dark at 1 atm air and at 23 °C for 30 min.

$$HBr + O_2 \longrightarrow Br^{\bullet} + OOH^{\bullet} \quad (4)$$

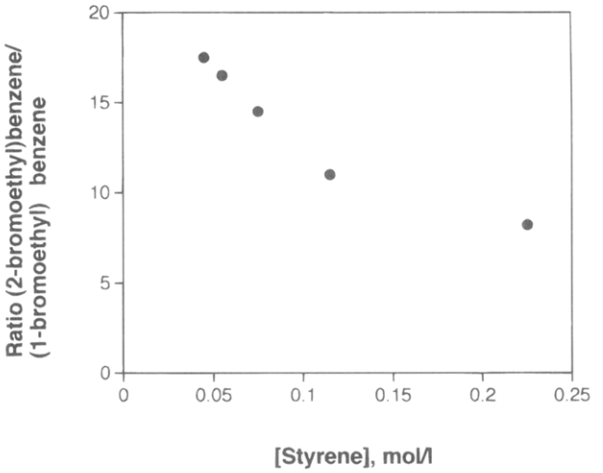

Figure 3. The ratio of (2-bromoethyl)benzene to (1-bromoethyl)benzene as a function of the styrene concentration. Reaction conditions: 1 M 2-bromo-2-methylpropanal, 0.75 M HBr, and styrene at various concentrations are reacted in 40 mL of ethyl acetate in the dark at 1 atm of air and at 23 °C for 30 min.

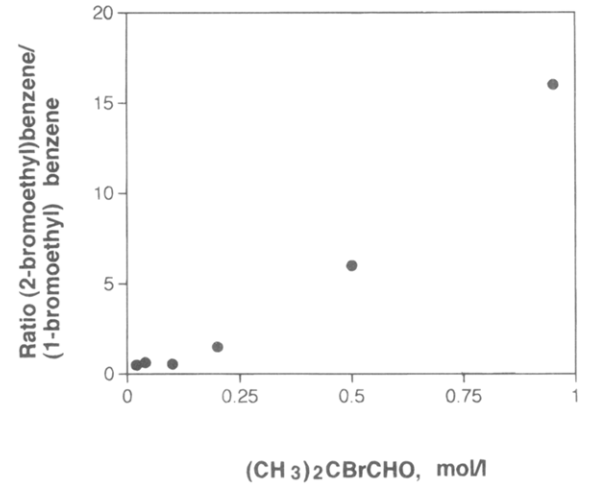

Figure 4. The ratio of (2-bromoethyl)benzene to (1-bromoethyl)benzene as a function of the hydrogen bromide concentration. Reaction conditions: 0.23 M 2-bromo-2-methylpropanal, 0.16 M styrene, and HBr at various concentrations are reacted in 40 mL of heptane in the dark at 1 atm of air and at 23 °C for 30 min.

The effect of the presence α-bromo carbonyl compounds in reactions performed with ethyl acetate as solvent is shown in Figure 1. On the one hand, one can clearly see that the α-bromo carbonyl compounds generally yielded high ratios of (2-bromoethyl)benzene *versus* (1-bromoethyl)benzene. On the other hand, the analogous hydrogen-substituted carbonyl compounds yielded a product mixture with a low (2-bromoethyl)benzene to (1-bromoethyl)-benzene ratio of 0.05−0.15 which is essentially unchanged from a reaction mixture containing no carbonyl additive. Interestingly, even the α-bromo carboxylic acid was effective in increasing the (2-bromoethyl)benzene to (1-bromoethyl)benzene ratio even though in a reaction mixture containing such a polar compound one may have expected an increase in the rate of the ionic reaction pathway and (1-bromoethyl)benzene as the major product. The electron-withdrawing carbonyl moiety could also be replaced with a cyano group as in bromoacetonitrile with similar results being obtained.

Further research was devoted to the use of 2-bromo-2-methylpropanal as promoter because of its relatively simple preparation[7] and the high yield of (2-bromoethyl)-benzene obtained. A survey of various solvents, Figure 2, showed that even in solvents generally ineffective for the anti-Markovnikov addition such as dioxane very considerable amounts of (2-bromoethyl)benzene were produced. Other reaction parameters were also tested, including the effect of the styrene concentration, Figure 3, the effect of the hydrogen bromide concentration, Figure 4, and the effect of the 2-bromo-2-methylpropanal concentration, Figure 5. It is clear that low concentrations of styrene are to be preferred with higher styrene concentrations leading to lower (2-bromoethyl)benzene to (1-bromoethyl)benzene ratios. There is, however, a clear advantage in using relatively high concentrations of hydrogen bromide and 2-bromo-2-methylpropanal which lead to high (2-bromoethyl)benzene to (1-bromoethyl)benzene ratios. The effect of the styrene and

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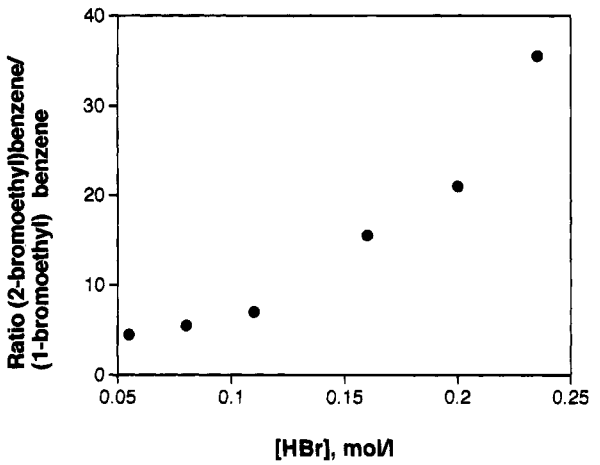
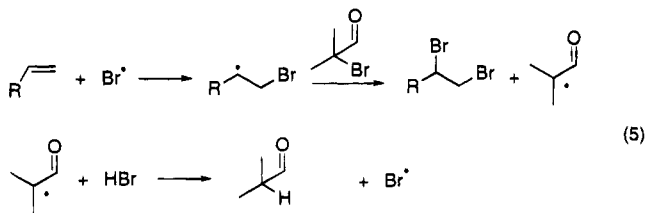


Figure 5. The ratio of (2-bromoethyl)benzene to (1-bromoethyl)benzene as a function of the 2-bromo-2-methylpropanal concentration. Reaction conditions: 0.75 M HBr, 0.23 M styrene, and 2-bromo-2-methylpropanal at various concentrations are reacted in 40 mL of ethyl acetate in the dark at 1 atm of air and at 23 °C for 30 min.

hydrogen bromide concentration on the product ratio is in agreement with results reported previously by others.[1,2,5] Importantly, at low concentrations of 2-bromo-2-methylpropanal it appears that 2-bromo-2-methylpropanal was not able to direct the reaction to formation of the anti-Markovnikov addition product. However, reactions performed in a continous reaction mode where hydrogen bromide and styrene were added continuously to a 0.11 M solution of 2-bromo-2-methylpropanal showed that product ratios of 100 to 200 (2-bromoethyl)benzene to (1-bromoethyl)benzene can be easily obtained. This result shows that the absolute concentration of 2-bromo-2-methylpropanal is not the determining factor, rather its concentration relative to the two reactants, styrene and hydrogen bromide. Varying reaction temperature between 23 °C and 60°C had almost no effect on the ratio of the addition products. For example, in a reaction mixture containing 0.25 M HBr, 0.25 M styrene, and 1 M 2-bromo-2-methylpropanal in ethyl acetate at 23 and 60 °C, yielded ratios of (2-bromoethyl)benzene to (1-bromoethyl)benzene of 16.0 and 19.6, respectively.

It would be enticing at this point to suggest that 2-bromo-2-methylpropanal and other α-bromo carbonyl compounds act as initiators[8] to form bromine radicals from hydrogen bromide through formation of acyl radicals. Such reactions are well known for ketones and aldehydes such as 2-butanone and acetaldehyde and often used in commerical oxidation operations.[9] There are, however, several lines of evidence that rule out such a possibility. First, as stated above no (2-bromoethyl)-benzene is formed under the *careful exclusion* of oxygen from the reaction mixture. Second, the addition of compounds such as 2-bromo-2-methylpropanoic acid, as shown in Figure 1, also increases the yield of (2-bromoethyl)benzene, although such compounds are not known to form acyl free radicals in thermal reactions. Third, the rather large quantaties of 2-bromo-2-methylpropanal required relative to the substrates seem to make it an unlikely candidate for an effective radical chain initiator. Finally, in the presence of atomospheric air, for hydrogen bromide addition to less active substrates such as 1-decene, no statistically significant effect on the amount of anti-Markovnikov addition product could be observed upon the addition of 2-bromo-2-methylpropanal. Thus, in a reaction mixture containing 1 M HBr and 0.25 M 1-decene in ethyl acetate at 23 °C, the ratio of 1-bromodecane/2-bromodecane was 15.0 whereas upon addition of 1 M 2-bromo-2-methylpropanal the ratio was 15.9. A second pathway by which 2-bromo-2-methylpropanal and analogous α-bromo carbonyl compounds could act to increase anti-Markovnikov addition would be through inhibition of the ionic pathway. Since the nonsubstituted compounds had no inhibitory effect, such an explanation neccessarily based on the polarity of the carbonyl functionality is highly unlikely. Looking, therefore, for an other explanation, we surmise that the 2-bromo-2-methylpropanal and its analogues allow the occasional formation of relatively stablized alkyl radicals (stabilized by the carbonyl or cyano moieties) via *radical* induced homolytic cleavage of the carbon–bromine bond, eq 5.



(5)

Formation of such radicals allows the extension of the free radical chain reaction and increases the overall yield of the (2-bromoethyl)benzene. In less active substrates, the relatively slow ionic reaction renders such an extension of the chain reaction of little importance. A key point in this rationalization is to understand the ability of the propagating radical, $PhCHCH_2Br$, to abstract bromine from α-bromo carbonyl compounds in competition with hydrogen bromide so as to sustain the radical chain, since gas phase thermochemical data indicate such a reaction to be 5 kcal/mol endothermal and relatively slow. Thermochemical-kinetic data show that the *gas phase* reaction of an allyl radical with hydrogen bromide has a log k (M, s units) of around 6 at room temperature.[10] The analogous reaction of the $PhCHCH_2Br$ radical with hydrogen bromide is 1–2 kcal/mol endothermal, hence has a log k of 5 or less.[11] In more *polar solvents the hydrogen bromide is stabilized* (perhaps by several kcal/mol depending on the solvent) further lowering the rate of the reaction of the propagating radical, $PhCHCH_2Br$, with hydrogen bromide. On the other hand, such a solvent effect is not probable for the α-bromo carbonyl compounds. The result is an increasing effect on the (2-bromoethyl)benzene/(1-bromoethyl)benzene ratio with solvent polarity. The data from Figure 2 show only a 3-fold effect in heptane, but much larger effects, up to a 140-fold increase, in dioxane, acetone, and ethyl acetate. Furthermore, for α-bromo ketones, Figure 1, the carbon–bromine bond strength is lower than that nonsubstituted ketones and is little effected by the degree of substitution at the carbon center[12] thus making the formation of

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Table 1. Cyclization of 6-Bromo-1-hexene in the presence of Various Additives

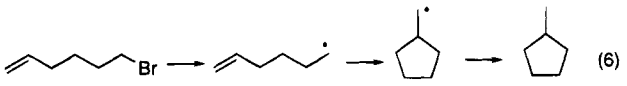
additive/initiator	yield of methylcyclopentane, mol %[c]	yield of 1-hexene, mol %[c]
AIBN	32.6	1.0
2-methylpropanal	18.1	1.3
2-bromo-2-methylpropanal	0.0	0.0
2-bromo-2-methylpropanal + AIBN[b]	0.8	0.0

[a] Reaction conditions: 0.25 mmol of 6-bromo-1-hexene, 0.125 mmol of tributyltin hydride, and 0.01 mmol of additive in 5 mL of dry benzene were heated to 70 °C for 90 min under nitrogen. [b] 0.01 mmol of both 2-bromo-2-methylpropanal and AIBN were used. [c] Yields were computed by GLC analysis as the mol % of 6-bromo-1-hexene converted.

stabilized radicals in the presence of neighboring electron-withdrawing groups feasible.

A reaction such as described by eq 5, also requires that 1,2-dibromoethylbenzene and 2-methylpropanal be formed over the course of the reaction.[13] Indeed, both these products are formed in trace amounts, 0.05–0.2%, although one cannot rule out the possibility that they were formed by other conceivable alternative pathways. For example, bromine radicals can react with hydrogen bromide to form molecular bromine which could add to styrene to yield (1,2-dibromoethyl)benzene. However, it is significant that in the absence of 2-bromo-2-methylpropanal no (1,2-dibromethyl)benzene formation was detected.

In order to shed more light on the function of α-bromo carbonyl compounds in a free-radical type reaction we tested the effect of 2-bromo-2-methylpropanal on the cyclization of 6-bromo-1-hexene to methylcyclopentane,[14] eq 6.



(6)

This reaction is known to take place with tributyltin hydride by a free-radical mechanism only. Such reactions are efficiently initiated by azobisisobutyronitrile (AIBN) to form the intermediate 5-hexen-1-yl radical which forms the methylcyclopentanyl radical in a fast cyclization reaction ($k = 10^5$ s^{-1}). In the presence of a hydrogen donor, in this case tributyltin hydride, methylcyclopentane is formed as major product along with 1-hexene as the minor product.[15] Results for the cyclization reaction under various conditions are summarized in Table 1. One can see that in the presence of AIBN, methylcyclopentane was easily formed. In a similar manner, 2-methylpropanal was also efficient in initiating the free-radical reaction. On the other hand, in the presence of 2-bromo-2-methylpropanal no reaction was observed. Finally, in the presence of both 2-bromo-2-methylpropanal and AIBN, there was some albeit slight formation of methylcyclopentane. Our explanation of these results is that as indicated above: (a) 2-bromo-2-methylpropanal does not thermally form acyl type radicals in appreciable amounts which initiate free-radical chain reactions; however, (b) 2-bromo-2-methylpropanal can react with radicals in this case thermally produced isobutyronitrile radicals to form stablized 2-methylpropanal radicals. The reaction of such a stabilized radical with a primary carbon–bromine bond to form a primary radical is not favored but nevertheless occasionally occurs yielding methylcyclopentane. In the case of the hydrogen bromide addition to styrene, the presence of stablized 2-methylpropanal radicals extends the free-radical chain via more formation intermediate bromine radicals by homolytic cleavage of hydrogen bromide thereby increasing the yield of (2-bromoethyl)benzene.

(13) Other possible products that could be formed by reaction of α-carbonyl radicals such as the dimer of the radical or the addition product of the dimer to the alkene were not dectected by the GC analysis.

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Conclusion

A methodology has been developed whereby α-bromo carbonyl compounds such as 2-bromo-2-methylpropanal can be used as promoters in the "abnormal" of anti-Markovnikov addition of hydrogen bromide to styrene. We have also shown that 2-bromo-2-methylpropanal is not the initiator of a free radical reaction, rather the mode of action of 2-bromo-2-methylpropanal is by radical-initiated formation of relatively stable 2-methylpropanal radicals which may increase the amount of free-radicals in the propagation stage thereby increasing the yield of (2-bromoethyl)benzene.

Experimental Section

Materials and Instruments. Solvents were of analytical purity and dried and distilled before use. Styrene was treated and distilled before used to remove polymerization inhibitors. All other compounds except 2-bromo-2-methylpropanal, 2-bromopropanal, and bromoacetone were obtained commercially and used without further purification. The former compounds were synthesized by the known literature procedure.[7] Analysis of reaction mixtures was performed by GLC using a HP-5890 equipped with a flame ionization detector. For hydrobrominations the column used was a 5% phenyl methyl silicone column (HP Ultra 2) of 25 m length, 0.2 mm i.d., and 0.33 μm film thickness. The components were separated using the following program. Initial temperature 80 °C for 5 min, heating at 15 °C/min up to 200 °C. The identity of the compounds was verified using available standards and cross-checked by GLC-MS (HP-5790A). The concentration of hydrogen bromide was determined by extraction into water and titration with silver nitrate. For the cyclization of 6-bromo-1-hexene a 2 m 1/8 in i.d. glass coumn packed with 15% OV-210 on acid-washed Chromosorb W was used for GLC analysis. The components were separated using the following program. Initial temperature 80 °C for 1 min, heating at 10 °C/min up to 200 °C.

Hydrobromination Reactions. A typical procedure for the batch hydrobromination of styrene consisted of loading a 100 mL three-necked flask (painted black) equipped with a magnetic stirrer, thermometer, gas inlet, and hydrogen bromide trap with 40 mL of solvent and the required amount of 2-bromo-2-methylpropanal or other additive. Gaseous hydrogen bromide was added after drying over P_2O_5. A 1 mL sample was taken to measure the HBr concentration, and the reaction was initiated by addition of styrene. After 30 min the styrene conversion was essentially quantitative. A 5 mL aliquot of the reaction mixture was washed three times with water, 5% $NaHCO_3$, and water, dried over Na_2SO_4, and then analyzed by GLC.

Cyclization of 6-bromo-1-hexene. The cyclizations of 6-bromo-1-hexene were carried out in the dark in 10 mL sealed ampules by adding 40.7 mg (0.25 mmol) of 6-bromo-1-hexene, 36.4 mg (0.125 mmol) of tributyltin hydride, and 0.01 mmol of additive to 5 mL of dry benzene under nitrogen. The ampules were placed in a 70 °C oil bath for 90 min and then cooled and analyzed by GLC.

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