

THE HYDROBORATION OF ENOL ACETATES DERIVED FROM ALIPHATIC KETONES THE DIRECTIVE EFFECT OF THE ACETOXY GROUP

A. SUZUKI, K. OHMORI and M. ITOH

Department of Chemical Process Engineering, Hokkaido University, Sapporo, Japan

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Abstract—A variety of enol acetates derived from aliphatic ketones was subjected to hydroboration by diborane under standard conditions in order to determine the directive effect of the acetoxy group substituted at vinyl carbon. It was found that the enol acetates rapidly consumed four hydrides, as compared against non-conjugated acetates, and the B atom added mainly at the β -position of the double bond. The directive effect of the acetoxy group to hydroboration was concluded as follows: (1) The steric hindrance exerts a remarkable influence on hydroboration, comparable to that of the usual olefins. (2) In enol acetates, α -addition of boron shows an increase over that of the corresponding alkyl substituted olefins. (3) In a set of *cis-trans* isomers, the compound with *cis*-relationship between two alkyl groups gives a lesser β -addition product.

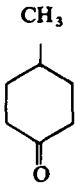
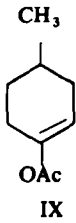
A CONSIDERABLE number of alicyclic enol acetate have been subjected to hydroboration-oxidation. For instance Hassner and Braun reported that the hydroboration-oxidation of cyclohexenyl acetate yields a 41% *trans*-1,2-cyclohexane diol and a 38% cyclohexanol.¹ Alvarey and Arreguin observed the conversion of steroid D-ring enol acetates to *trans*-diols in 40 to 50% yields.² Cagligoti *et al.* also converted a number of steroidal enol acetates into the corresponding *trans*-diols.³

On the other hand, the situation becomes complicated for aliphatic enol acetates. For example, the hydroboration of isopropenyl acetate exhibits a rapid uptake of 4.0 equivalents of hydride per mole of compound.⁴ Oxidation produces 1- and 2-propanol in the ratio corresponding to the hydroboration of propylene. Consequently, the reaction seems to involve hydroboration at the terminal β -position ($1H^-$), elimination of an acetoxyboron moiety, rehydroboration of the propylene ($1H^-$), and reduction of the acetoxyboron moiety to the alcohol stage ($2H^-$). Recently, Brown and Sharp reported on the hydroboration of isobutenyl, 1-butenyl, 2-butenyl and 1-cycloalkenyl acetates at 0°.⁵ They indicated that hydroboration of isobutenyl acetate proceeds comparatively slowly, placing practically all of the boron in the α -position, and the α -substituted derivative is readily oxidized to the corresponding aldehyde. With a decreasing tendency of the parent hydrocarbon to direct boron to the α -position, hydroboration gave lesser simple results, the addition proceeding to place boron at both the α - and β -positions. The directive effect of the acetoxy group, however, has so far not been given, because the situation is complicated by the ability of the β -boron derivatives to undergo elimination and rehydroboration and by the tendency of the α -boron derivatives to undergo replacement of the substituent by hydrogen.

TABLE I. PRODUCT DISTRIBUTION OF ENOL ACETATES AND THEIR NMR DATA IN CCl_4

Ketone	Enol acetate	Distribution, %	NMR spectra of enol acetate (τ)	
			Vinyl proton at β - position to acetoxy group	other protons
$\text{Me}-\text{C}(=\text{O})-\text{Me}$	$\text{CH}_2=\text{C}(\text{Me})\text{OAc}$ I	—	5.38 <i>cis</i> 5.31 <i>trans</i> 5.50	$\text{C}=\text{C}-\text{CH}_3$ 8.08 $\text{O}-\text{COCH}_3$ 7.93
$\text{Et}-\text{C}(=\text{O})-\text{Et}$	$\text{Me}-\text{C}(\text{OAc})=\text{C}(\text{Et})\text{H}$ II	65	5.03 5.10 (benzene)	CH_2-CH_3 9.00 (t) $\text{C}=\text{C}-\text{CH}_3$ 8.54 (d) $\text{O}-\text{COCH}_3$ 7.93
	$\text{Me}-\text{C}(\text{OAc})=\text{C}(\text{Et}')\text{H}$ III	35	5.00 4.87 (benzene)	CH_2-CH_3 9.03 (t) $\text{C}=\text{C}-\text{CH}_3$ 8.36 (d) $\text{O}-\text{COCH}_3$ 7.96
$\text{Me}-\text{C}(=\text{O})-\text{Pr}^a$	$\text{Me}-\text{C}(\text{AcO})=\text{C}(\text{H})\text{Et}$ IV	47	5.15	CH_2-CH_3 9.08 (t) $\text{C}=\text{C}-\text{CH}_3$ 8.22 $\text{O}-\text{COCH}_3$ 7.97
	$\text{Me}-\text{C}(\text{AcO})=\text{C}(\text{Et})\text{H}$ V	18	5.02	CH_2-CH_3 9.06 (t) $\text{C}=\text{C}-\text{CH}_3$ 8.13 $\text{O}-\text{COCH}_3$ 7.84
$\text{Me}-\text{C}(=\text{O})-\text{Pr}^1$	$\text{CH}_2=\text{C}(\text{OAc})\text{Pr}^a$ VI	35	5.41	CH_2-CH_3 9.00 (t) $\text{O}-\text{COCH}_3$ 8.01
	$\text{Me}-\text{C}(\text{AcO})=\text{C}(\text{Me})\text{Me}$ VII	33	—	$\text{C}=\text{C}-\text{CH}_3$ 8.17, 8.28, 8.46 $\text{O}-\text{COCH}_3$ 7.92
$\text{Me}-\text{C}(=\text{O})-\text{Pr}^1$	$\text{CH}_2=\text{C}(\text{OAc})\text{Pr}^1$ VIII	67	5.27	$\text{CH}-(\text{CH}_3)_2$ 8.90 (d) $\text{O}-\text{COCH}_3$ 7.77

TABLE 1—*continued*

Ketone	Enol acetate	Distribution, %	NMR spectra of enol acetate (τ)	
			Vinyl proton at β - position to acetoxy group	other protons
		—	4.78	$-\text{CH}-\text{CH}_3$ 9.01 $\text{O}-\text{COCH}_3$ 7.97

In order to determine the true directive effect of the acetoxy group for hydroboration, hydroboration for a variety of enol acetates derived from aliphatic ketones was attempted.

RESULTS AND DISCUSSION

Preparation and identification of enol acetates. In the present work, all the enol acetates were produced by the reaction of isopropenyl acetate with the corresponding ketones in the presence of *p*-toluene sulphonic acid.⁶ The enol acetates thus obtained were isolated and purified by preparative chromatographic procedure. The product distribution of enol acetates is summarized in Table 1.

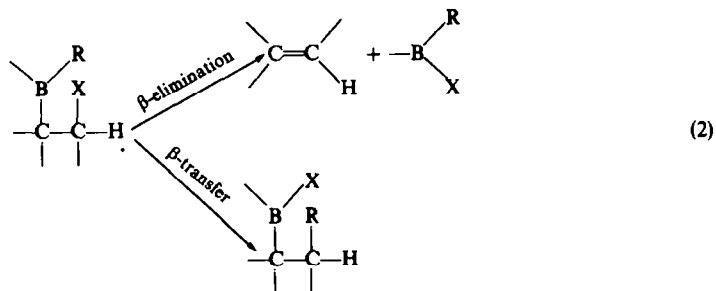
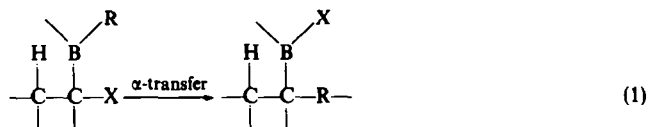
The structures of the enol acetates were determined with their NMR spectroscopic data. In enol acetates⁷ and enol ethers,⁸ it is known that the vinyl protons having a *cis*-relationship to the acetoxy or the ether group, resonate in a lower magnetic field, in comparison with the corresponding *trans*-isomers. The structures of enol acetates (II, III, IV and V) were assigned respectively by this method.* In the case of 3-acetoxy-2-pentenes, (II) and (III), a remarkable difference between the vinyl protons ($\Delta = 5.10 - 4.87 = 0.23$ ppm), was observed in benzene solution, whereas it was only 0.03 ppm ($\Delta = 5.03 - 5.00$) in carbon tetrachloride. In the case of enol acetate derived from methyl *n*-propyl ketone, each of IV and V was not isolated in a pure state. Consequently, the structures, (IV and V) were determined by a comparison of the NMR peak areas due to the respective type protons in the mixture.

Hydroboration of enol acetates. The first example of the reaction of a vinyl derivative with diborane under representative hydroboration conditions has been carried out for vinyl chloride.¹⁰ The authors concluded that the hydroboration of vinyl chloride proceeds to place the boron predominantly on the β -carbon to the substituted Cl atom.

* Another procedure to determine such structural relationships has been published. Namely this was based upon a comparison of the spin-spin coupling constant in the structure $\text{H}_x-\text{C}=\text{C}-\text{C}-\text{H}_y$. According to Fraser's results,⁹ the $J_{x,y}$ of the compound with a *trans*-configuration between H_x and H_y is slightly smaller (about 0.2 c/s) than that of the corresponding *cis*-isomer. However, a generalization was not applied to the characterization of the isomeric enol acetates obtained in the present work, because the distinction is so small.

The same results were observed in the hydroborations of ethyl vinyl ether¹¹ and the piperidine enamine derivative of cyclohexanone.¹² On the other hand, it has been found by Seyferth^{13, 14} that in an addition of borane to trimethylvinylsilane, the distribution of the boron between the α - and β -positions of the double bond was 59:41. Shortly afterward Brown and his research group started their systematic studies on the hydroboration of substituted styrenes and revealed that the boron distribution to α - and β -positions in the double bond was markedly influenced by the nature of the substituents.¹⁵ More recently, they reported that the effect of the substituent in controlling the direction of hydroboration of such styrenes is related to the σ^+ values of the substituents.¹⁶ Such a directive effect by substituents has been observed in the case of dialkylvinylboronate.¹⁷

Pasto *et al.* have indicated that substantial formation of α -substituted organoboranes occurs in many cases where the hetero-functional group is ethoxy,¹⁸ phenylmercapto¹⁹ and halo.^{20, 21} The types of reactions of α - and β -heterosubstituted organoboranes shown by the authors are summarized below.



The olefin formed in the β -elimination may undergo subsequent hydroboration. Consequently, they concluded that it is very difficult to distinguish between an addition-elimination-hydroboration-sequence and an addition-transfer reaction sequence.

Hydroboration studies on vinyl derivatives with acetoxy group as a substituent which have been previously reported, were shown in the introduction of this paper. The directive effect of acetoxy group, however, has not been given.

In order to examine the reaction of enol acetate with diborane, isopropenyl acetate was firstly employed as a sample. It was confirmed that the hydroboration of the acetate with diborane at 25° exhibits a rapid uptake of 4 equivalents of hydride per mole of the compound, as it has been already observed.⁴ The results are shown as follows:

Reaction time (min)	5	10	20	90	240
H ⁻ /isopropenyl acetate	4.02	3.95	4.07	4.05	4.08

The rate of hydride consumption of isopropenyl acetate was much faster than the earlier results with crotyl acetate²² and 3-acetoxy cyclopentene²³ which have an acetoxy group at allylic carbon.

The effects of reaction temperature and of the amount of hydride added in the reaction, are summarized in Table 2. In the case of enol ether,¹⁸ it was shown that the

TABLE 2. HYDROBORATION-OXIDATION OF ISOPROPENYL ACETATE

Added H ⁻ (H ⁻ /acetate)	Reaction temp and time	Yield of alcohols (%)			Acetate recovered, %
		1-PrOH	2-PrOH	EtOH	
1	0°C, 4 hr.	22	1	15	77
8	0°C, 4 hr.	96	4	81	0
8	22°C, 4 hr.	97	3	94	0

product ratio of hydroboration is changed by the reaction temperature employed. Whereas, in the hydroboration of isopropenyl acetate, a large difference of the product yield was not observed at 0° and 22°. Consequently, the enol acetates were hydroborated with a large excess of diborane (8 equivalent hydrides per enol acetate) at 22°. After maintaining the reaction temperature, the reaction mixtures were oxidized by the usual procedure²⁴ with alkaline hydrogen peroxide, and then the reaction products were analysed by GLPC. The results are summarized in Table 3.

TABLE 3. HYDROBORATION-OXIDATION OF ENOL ACETATES

Enol acetate	Yield of mono-ol, %	Distribution of mono-ol, %		Used H ⁻ (H ⁻ /ester)	Directive effect, %	
		1-ol	2-ol		α	β
I	87	93	7	4.1	1	99
VI	75	82	18	4.0	13	87
VIII	86	84	16	3.8	9	91
II	90	45 ^a	55 ^b	4.2	15	85
III	90	38 ^a	62 ^b	4.0	28	72
IV	75	68 ^a	32 ^b	4.1	32	68
V	75	73	27	3.9	37	63
VII	86	100	0	4.0	(100)	(0)
IX	55 ^c	25 ^d	75 ^e	4.3	—	—

^a 2-ol.

^b 3-ol.

^c In this case, two diols were obtained in a yield of 18%, but the structural assignment was not determined.

^d 3-ol.

^e 4-ol.

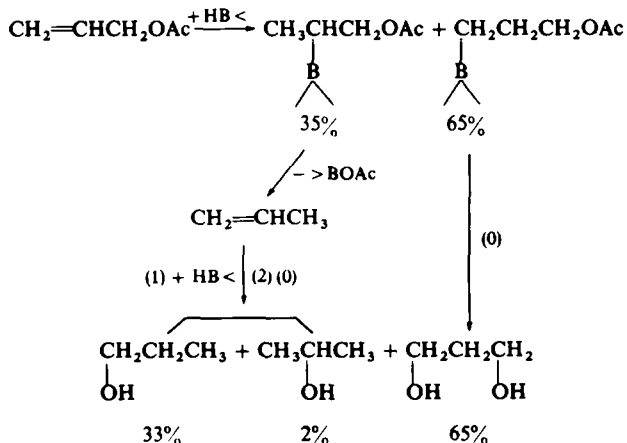
Elimination reaction of β-acetoxy organoboranes and reduction of α-acetoxy organoboranes. It has been suggested that the direction of addition of the boron-hydrogen moiety to substituted olefins is determined by both steric and electronic influences.²⁵

Consequently, the direction of addition to such olefins would be determined by the relative stability of the two possible transition states X and XI. An electron-withdrawing substituent would be expected to favor transition state XI at the cost of X.

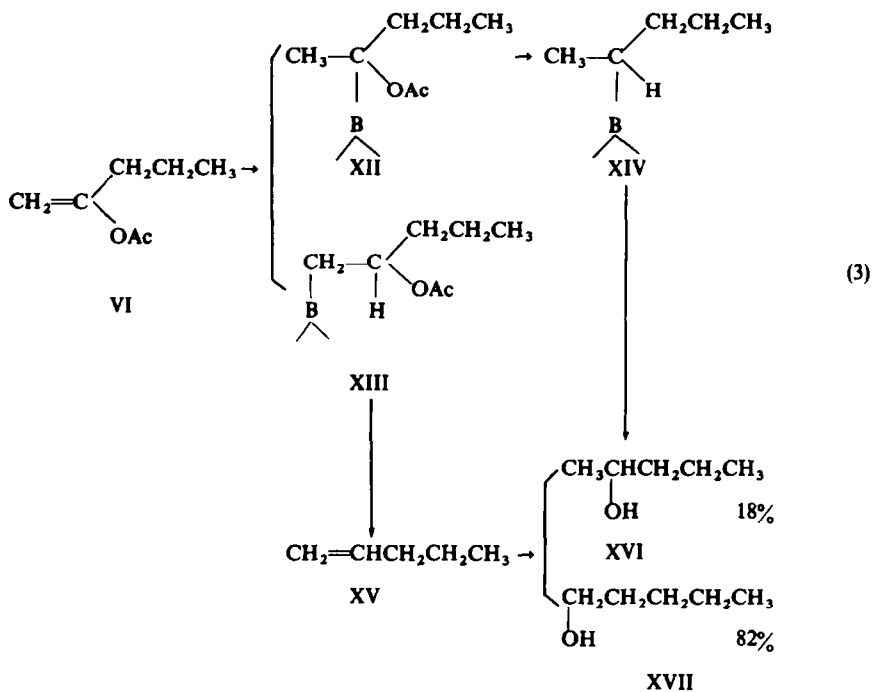


In the case of enol acetates, it is impossible to expect a simple conclusion for the electronic influence, because the acetoxy group has both effects, +R and -I.

Other difficulties to determine the directive effect of acetoxy group are, as previously described, the facts that the α -boron derivatives tend to be replaced by hydrogen and the β -boron derivatives have a tendency to undergo elimination and rehydroboration. In regard to the β -boron derivatives, Pasto *et al.*¹⁹ suggested another transfer, "β-transfer", as shown in Eq. 2. However, this is now contradicted, at least in the case of enol acetates for the following reason. Previously Brown and Cope²⁶ reported that in the hydroboration of allyl acetate since the product distribution is 65% 1,3-propanediol and 35% 1-propanol, 65% of the boron adds to the terminal C atom of the double bond and the remainder of the addition takes place on the secondary C atom. And the formation of 1-propanol was explained by the assumption that 1-acetoxy-2-propyl borane should be followed by a rapid elimination to give propylene, which is then rapidly hydroborated and the organoborane thus formed gives 1-propanol by oxidation. If this assumption is correct, the product distribution should be 65% 1,3-propanediol, 33% 1-propanol and 2% 2-propanol, because the hydroboration of authentic propylene gives a product distribution of 94% 1-propanol and 6% 2-isomer. The existence of 2-propanol was not described in the paper. In order to ascertain the existence of 2-propanol, we carefully analyzed the reaction mixture obtained from allyl acetate by Brown's method using GLPC, and found that the alcohol is included at a 2% distribution. Therefore, "β-transfer" process for the β -substituted organoboranes proposed by Pasto should be ruled out in the case of enol acetates.



On the other hand, it is impossible to assume that all the monohydric alcohols are yielded by a secondary hydroboration of the olefins which were obtained by elimination of β -acetoxy organoboranes first formed. For example, although the enol acetate (VI) is converted to 82% 1-pentanol and 18% 2-pentanol by hydroboration-oxidation reaction, the distribution should be 94 : 6, judging from the elimination-rehydroboration mechanism. Thus we wish here to propose the following mechanism as shown in Eq. 3, to explain monoalcohol formation.



In regard to α -substituted organoboranes, it has been reported that such organoboranes achieve removal of the functional group and its replacement by hydrogen and that the reaction proceeds through " α -transfer" mechanism, which involves an intramolecular exchange of hydrogen and other functional groups.^{18-21, 27} Recently, we confirmed that this kind of reaction proceeds in terms of a nucleophilic reduction in the case of enol acetates derived from aldehydes.²⁸ Consequently, we believe that 2-pentanol (XVI) can be obtained by both ways, one of which is as a hydroboration product of 1-pentene (XV) which is yielded by elimination of the β -acetoxy borane (XIII), and another is from the nucleophilic reduction product (XIV) of the α -acetoxy borane (XII), while 1-pentanol (XVII) should be only produced by rehydroboration of 1-pentene. According to this mechanism, the molar fraction toward β -addition of boron, x in 2-acetoxy-1-pentene (VI) is calculated by the Eq. $0.94x = 0.82$. The directive effect is calculated with hydroboration data of the parent olefin²⁴ by the same manner and the results are summarized in Table 3.

Directive effect. As described in the two possible transition states X and XI, it has been suggested that the direction of the boron-hydrogen moiety to the olefins with a

functional group, Y is determined by both steric and electronic influences,¹⁵ and such an addition reaction proceeds through a 4-center transition state.²⁹ From the results which are summarized in Table 3, the directive effect of acetoxy group to hydroboration is concluded as follows: (A) The steric hindrance gives a remarkable influence to the directive effect of acetoxy group in enol acetates, similar to the cases of other olefinic compounds. (B) In the enol acetates, α -addition of boron is increased, as compared with the corresponding alkyl substituted olefins; for example, the relationship between the enol acetate (II) and a trialkyl substituted ethylene. (C) In a set of *cis-trans* isomers, the compound which has a *cis*-relationship between two alkyl groups gives a less β -addition product than in the case of the corresponding *trans*-isomer. For example, in the addition of boron to *trans*-3-acetoxy-2-pentene (II), the distribution of the boron between the α - and β -positions of the double bond is 15:85, whereas in the corresponding (III), the ratio is 28:72. Similarly, in a set of enol acetates (IV and V), the distribution ratios are 32:68 and 37:63, respectively. Since the inductive effect of acetoxy group, $-I$ is same in these cases, the differences of the addition ratio of boron should be due to the difference of the $+R$ effect of the acetoxy group. As the effect is disturbed in the case of enol acetate with a *cis*-structure between two alkyl groups, the β -addition might be decreased.

EXPERIMENTAL

Preparation of the enol acetates. The authentic samples of the enol acetates (Table 1) were prepared by reaction of the ketones with isopropenyl acetate in the presence of *p*-toluenesulphonic acid.⁹ The following procedure is representative.

A mixture of 5.74 g (66.7 mmoles) diethylketone, 10.0 g (100 mmoles) iso-propenyl acetate and 130 mg *p*-toluenesulphonic acid was refluxed in a round bottomed flask with Vigreux column to distil off the acetone formed. The reaction mixture was cooled and poured into a cold mixture of sat NaHCO_3 aq and

TABLE 4. THE PHYSICAL PROPERTIES AND ELEMENTAL ANALYSES OF ENOL ACETATES DERIVED FROM KETONES

Enol acetate	n_D^{20}	b.p., C° (mmHg)	Elemental analysis			
			Calcd.		Found	
			C	H	C	H
I	1.4006	96.6 (748)	—	—	—	—
II	1.4171	125.0 (763)	65.59	9.44	65.42	9.48
III	1.4202	131.5 (763)	65.59	9.44	65.63	9.27
IV, VI	1.4153	121.0 (764)	65.59	9.44	65.38	9.38
V	1.4195	122.0 (764)	65.59	9.44	65.50	9.52
VII	1.4222	121.0 (763)	65.59	9.44	65.45	9.67
VIII	1.4119	114.0 (763)	65.59	9.44	65.66	9.46

pentane. The pentane layer was dried and concentrated and samples of *trans*-II and *cis*-III were collected by distillation, b.p. 120–135°, containing 65% of II and 35% of III. The pure samples were obtained by gas chromatography. The physical properties and elemental analytical data are presented in Table 4.

The composition of isomers was determined by means of gas chromatographic and NMR analytical methods. In cases which were not completely separated even in GLPC analysis as in the case of the enol acetates IV and VI, the composition was decided by the NMR method alone.

The stereochemical assignments made to the various pairs of geometric isomers listed in Table 1 are based on comparison of the NMR spectra of each pair of isomers in CCl₄ soln. Although in CCl₄ soln, the NMR signals for the vinyl protons of I, II, and III were shown to draw on, the peaks were well separated in benzene soln.

The physical properties and NMR data for other enol acetates are listed in Table 4 and 1, respectively.

Purification of solvents and preparation of diborane. Purification of diglyme, THF and BF₃-etherate, and the preparation of diborane in THF soln were carried out by the usual procedure.¹⁴

General procedure of hydroboration-oxidation of enol acetates. All glassware used in the experiments was flamed out in a stream of dry N₂ before use. All hydroborations were carried out in a 3-necked 100 ml round-bottomed flask with a thermometer, a water-cooled reflux condenser, inlet tube fitted with a rubber septum and a Teflon-coated magnetic stirring bar.

The representative procedure is as follows: A 5 ml THF soln containing 30 mmoles isopropenyl acetate was added to 80 mmoles borane in 20 ml tetrahydroborane at 22° during 3 min. The soln was stirred at room temp. After 4 hr, 5 ml water was injected into the reaction mixture. The volume of gas evolved was measured in a gas buret. The amount of hydride consumed was the difference between the amount started with and the amount left in soln.

Oxidation was carried out by adding 30 ml of 3N NaOH, followed by a dropwise addition of 30 ml of 30% H₂O₂. At this point the internal standard was added. The soln was then saturated with K₂CO₃ and separated. The ether layer was dried over MgSO₄ and analysed by GLPC.

The Hitachi KGL-2A with a 50m capillary Carbowax 20M column was used for product analysis and Ohkura GT-360 with a 2m column packed with 20% Carbowax 20M on diasolid 60/80 was used to separate products.

The mono-ols thus obtained, 1- and 2-propanol, 1-, 2- and 3-pentanol, 3-methyl-1- and -2-butanol were confirmed by direct comparisons with those of the authentic samples (Tokyo Kasei Kogyo Co. Ltd.).

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