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Protonation and Deprotonation of Enamines. II. Conversion of Isomeric Enamines Derived from Unsymmetric Methyl Ketones and Morpholine into the Least Substituted Isomer by Regioselective Deprotonation of Immonium Salts

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Enamines derived from morpholine and alkyl methyl ketones (alkyl = propyl, hexyl, isobutyl, neopentyl, 2-phenylethyl, benzyl isopropyl, cyclopropyl cyclopentyl and cyclohexyl) were transformed to the corresponding immonium trifluoroacetates on treatment with trifluoroacetic acid in pentane. With the exception of the immonium salt from benzyl methyl ketone all immonium salts afforded the enamine isomer with a terminal double bond on treatment with either one equivalent of *tert*-butylamine or secondary amine by a regioselective deprotonation of the immonium ion. The selectivity was lower with n-alkyl methyl ketone enamines. The nature of base and the solvent is discussed. Directions for synthetic application of the method are given.

Enamines have been subjected to extensive investigations and the number of synthetic applications of these compounds is considerable.[1] However, most studies in the enamine field have been devoted to enamines derived from cyclic ketones, aldehydes and to heterocyclic enamines. The references concerning enamines from acyclic ketones are remarkably few in number.

Methyl ketone derived enamines have long been considered as unstable and prone to self-condensation reactions.[2–5] The advent of the synthetic method using titanium tetrachloride as water scavenger and catalyst [6] opened up a route to these compounds. Despite their availability, the enamines from unsymmetric methyl ketones seem to have attracted little interest. One probable reason for this is the fact that unsymmetric ketones with both α and α′ hydrogens usually give rise to mixtures of isomeric enamines differing in double bond position (Fig. 1). Factors influencing the isomer distribution have been studied by several authors.[7,18]

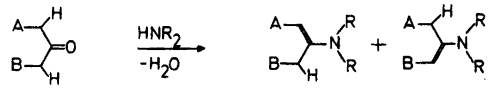
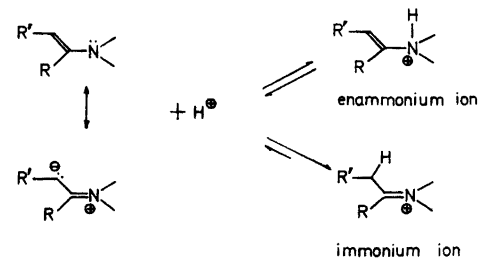


Fig. 1. Syntheses of isomeric enamines.

The conjugation of the nitrogen lone pair with the π-system gives enamines some character of ambident nucleophiles so that protonation can give rise to two different products: Protonation on nitrogen forming an enammonium ion or on β carbon forming an immonium ion, (Scheme 1). It has been demon-



Scheme 1.

strated that *N*-protonation is rapid and that the enammonium ion more or less slowly rearranges to the more stable immonium ion.[8–12] Protonation of isomeric enamines from unsymmetric ketones under equilibrating conditions will thus give a common immonium ion. Selective protonation of one isomer present in a mixture has been reported from this laboratory,[13–14] and a separation of the tetrasubstituted isomer in Fig. 2 by selective hydrolysis of the trisubstituted isomers [15] probably reflects a selectivity in protonation during hydrolysis.

The acid-catalyzed isomerisation of enamines probably proceeds *via* an immonium ion intermediate. Kinetic studies on the isomerisation of enamines from 1-methyl-2-indanone have been reported by Edlund *et al.*[16–18] and qualitative results concerning other ketones have been reported by various authors.[15,19–22]

It has been observed that enamine synthesis from unsymmetric ketones sometimes gives rise to only one isomer as a kinetically controlled product.[6,18,21] The finding [23] that 2-pentanone gives only 2-(4-morpholinyl)-2-pentene when prepared by azeotropic distillation for 96 h in the presence of *p*-toluenesulfonic acid appears somewhat suspect.

If immonium ions are intermediates (as is generally accepted [1]) in the reaction sequence forming enamines by the condensation of secondary amines with ketones, the finding of one isomer as the kinetically controlled product indicates a difference in the kinetic acidity of the α- and α′-protons in unsymmetric immonium salts. If this is a general feature it should be possible to prepare an immonium salt by protonation of isomeric enamines and obtain the kinetically favoured isomer by treatment with base. In a previous investigation using isopropyl methyl ketone enamines [13]

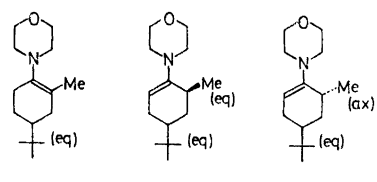
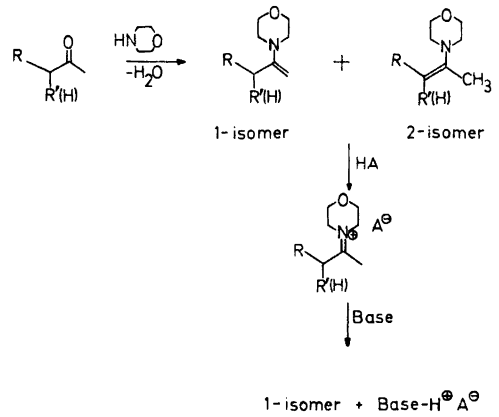


Fig. 2. Tetra- and trisubstituted isomers.



Scheme 2.

we were able to confirm a difference in the kinetic acidity between α- and α′-protons in the morpholine immonium salt; the methyl protons being the more acidic. If these properties are common to other morpholine enamines from methyl ketones a protonation – deprotonation sequence as shown in Scheme 2 will offer a means for transforming a mixture of isomeric enamines into the isomer with a terminal double bond. In the following paragraphs this isomer is called the 1-isomer; the isomeric enamine will be called the 2-isomer.

A number of methyl ketone – morpholine enamines have been prepared and treated as shown in Scheme 2. The enamines studied were obtained from both primary and secondary alkyl (cycloalkyl) methyl ketones.

RESULTS AND DISCUSSION

Isomer distribution at equilibrium. The room temperature equilibrium distribution of isomeric enamines obtained from the ketones studied are shown in Table 1. Some of the results require some discussion: Because of severe crowding in the 2-isomer *methyl neopentyl ketone* gives only the 1-isomer. This result is surprising since the isobutyl methyl ketone which is not very much different gives an almost equal distribution of the two isomers. The fact that *benzyl methyl ketone* gives only the 2-isomer can be rationalized in terms of conjugation with the aromatic ring. *Cyclopropyl ketone enamines* have been reported previously and these ketones seem to

Table 1. Room temperature equilibrium distribution of enamine isomers.

Starting ketone, $RCOCH_3$ R=	Distribution/% 1-Isomer	2-Isomer	Solvent [a]
Propyl	35	65	A, B
Hexyl	32	68	A, B
Isobutyl	51	49	A
Neopentyl	100	0	A
2-Phenylethyl	30	70	A
Benzyl	0	100	A, C
Isopropyl	29	71	A, B, C
Cyclopropyl [b]	100	0	C
Cyclopentyl	9	91	A
Cyclohexyl	65	35	A
	78	22	C

[a] A, pentane; B, benzene; C, deuteriochloroform. [b] From Ref. 24.

give only the vinyl cyclopropane isomer. Cyclopropylidene isomers have not been found [24] as yet. The difference in isomer distribution between the *cyclopentyl* and *cyclohexyl* ketone enamines is in accord with the generalisation by Brown on the stability of exocyclic double bonds to five- and six-membered rings.[25]

Spectra of immonium salts. The chemical shift of the $C=N^+$ in the ^{13}C NMR spectrum appears in the region, 188 – 195 ppm. We also found that the counterion does not influence the chemical shift which is in agreement with a recent report.[26] IR spectra obtained from both chloroform solutions and Nujol mulls show strong absorption in the region 1640 – 1680 cm^{-1}.[27] We interpret these findings as proof of an ionic structure of immonium salts even in hydrocarbon suspension.

Deprotonation of immonium ions. The literature concerning enamine basicity is confusing and sometimes contradictory.[28,29] Hinman [29] has proposed that the base strength of the enamines compared with the saturated analogues is dependent on the structure of these molecules. Thus α-alkyl substituents are base strengthening while β-alkyl substituents are base weakening. If this generalisation were valid for other than aqueous systems, deprotonation of immonium salts to the 1-isomer should be *a priori* a very improbable reaction with amine bases. The 1-isomers are lacking base weakening β-substituents and would be expected to be stronger bases than saturated amines. As previously reported by us,[18] immonium salts from methyl isopropyl ketone enamines are, in fact, deprotonated by amine bases when using equimolar amounts of base. Diisopropylamine was found to be selective and gave only the 1-isomer, whereas trimethyl- or triethylamine showed no selectivity and gave mixtures of both isomers. We concluded that steric hindrance of attacking base is essential for selective deprotonation. This conclusion was not quite correct; see below. It was assumed that by increasing the steric bulk of the attacking base the less steric demands of primary alkyl groups could be compensated for, to give selective deprotonation of primary alkyl ketone derived immonium salts.

Model experiments on methyl isobutyl ketone – morpholine enamine. Initial experiments with the immonium trifluoroacetate showed a selective formation of the 1-isomer when the immonium salt was reacted with diisopropylamine in pentane. Neither triethylamine nor hexamethyldisilazane were selective, the latter being more sterically hindered than diisopropylamine. To study these somewhat puzzling results, twelve different amine bases were selected, allowing a variation in both basicity and steric hindrance. Table 2 shows that, at 0 °C in pentane, addition of one equivalent of base gave deprotonation with all bases used. However, selectivity was found only with primary and secondary amines, an observation similar to that which was found with methyl isopropyl ketone immonium salt.[18] With propylamine and, to some extent, with isopropylamine a nucleophilic attack of the base on the immonium group competes with deprotonation (see below). *tert*-Butylamine gave a selective deprotonation. A nucleophilic addition of this amine to the immonium group is likely to be disfavoured for steric reasons. The secondary amines with the exception of hexamethyldisilazane were all selective. It is noted that tetramethylpiperidine gave a somewhat lower selectivity than the other less hindered secondary amines. Thus, for selectivity, it seems to be essential that the base possesses at least one hydrogen atom on the nitrogen; further, that selectivity is reduced or lost completely with too much steric hindrance. A certain amount of steric hindrance is necessary in

Table 2. Different amine bases tested in pentane as solvent for deprotonation of immonium trifluoroacetate from methyl isobutyl ketone – morpholine enamine.

Amine base	Isomer distribution, % 1-Isomer	2-Isomer	Yield, %
Primary amines			
Propylamine	53	47	[a]
Isopropylamine	64	36	[a]
tert-Butylamine	100	0	95 – 100
Secondary amines			
Morpholine	100	0	74
Piperidine	100	0	96
Diisopropylamine	100	0	80 – 90
Hexamethyldisilazane	55	45	50
2,2,6,6-Tetramethylpiperidine	94	6	100
Tertiary amines			
Triethylamine	51	49	75
N-Methylmorpholine	50	50	60
N-Methylpiperidine	53	47	70
N-Ethyldiisopropylamine	50	50	70

[a] Yields not reproducible due to nucleophilic attack by the base on the immonium ion.

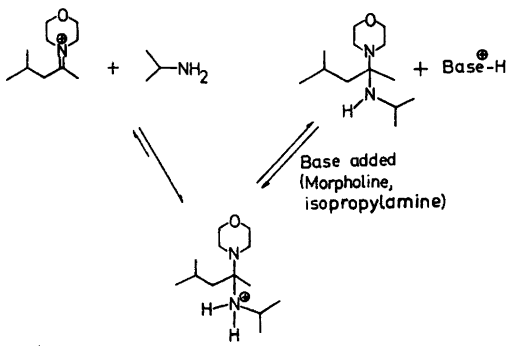
primary amines to suppress a nucleophilic attack on the immonium ion. The reaction was performed in a heterogeneous system with the immonium salt suspended in pentane. For this reason no kinetic information is obtainable. At present, the experimental results do not permit us to give an acceptable mechanistic explanation for the selectivity.

Deprotonation with the amines in Table 2 was also studied in other solvents: chloroform, benzonitrile and *tert*-butylbenzene (the latter was chosen in place of benzene to make a comparison possible with the experiments performed in pentane at 0 °C). In neither solvent was the reaction found to be selective under conditions which gave selectivity in pentane. However, isolated (85 %) 1-isomer was found to isomerize rapidly in these solvents, therefore preventing any conclusion as to the selectivity of the deprotonation to be made. The rate of isomerisation was lowered by the addition of a large excess of base in accord with observations on other enamines.[16,17,21] Using chloroform and benzonitrile homogeneous reaction mixtures were obtained. In *tert*-butylbenzene the amine salt formed and the starting immonium salts were somewhat soluble. In pentane the salts are insoluble. The high rate of isomerisation is probably due to the solubilization of the acid species present in these solvents. In pentane, ionic species are only slightly soluble and the observed excellent selectivity in this solvent is aided by this factor. Using five equivalents of either *tert*-butylamine or diisopropylamine 100 % selectivity was found in chloroform at – 60 °C. Use of higher temperature and/or one equivalent of base gave lower or no selectivity. Triethylamine was not selective in chloroform.

Some findings concerning the occurrence of deprotonation of the immonium salt using different bases in chloroform, benzonitrile and *tert*-butylbenzene can be given, thus providing information of the relative basicity: amine – enamine in these solvents. Deprotonation using hexamethyldisilazane did not occur in these solvents while the yields in pentane were *ca.* 50 %. Hexamethyldisilazane is therefore considered to be a weaker base than the enamine. *N*-Methylmorpholine did not give any deprotonation in *tert*-butylbenzene or benzonitrile. In chloroform deprotonation occurred but coincidence in the ^{1}H NMR spectrum of the resonance signals from the enamine vinyl protons (1-isomer) and morpholinyl group and those from the base made quantitative interpretation uncertain.

In all solvents studied propylamine and isopropylamine were observed to take part in nucleophilic attack on the immonium ion. In pentane this is competitive with deprotonation whereas in chloroform, benzonitrile and *tert*-butylbenzene it is the dominating reaction. The reaction with isopropylamine in benzonitrile was studied by ^{1}H NMR. The changes in chemical shift following addition of, respectively, morpholine, isopropylamine, morpholinium trifluoroacetate and isopropylammonium trifluoroacetate to the reaction mixture are consistent with the reactions shown in Scheme 3.

Adaptation of the protonation – deprotonation reaction for preparative purposes. Hydrogen chloride treatment of enamines usually affords crystalline immonium salts, but hydrogen chloride has the disadvantage that it is difficult to apportion. Perchloric acid affords perchlorates that are explosive and therefore less well-suited as synthetic intermediates. Anhydrous fluoroboric acid purchased in ether solution is rather expensive. Treatment of the enamines in Table 1 with trifluoroacetic acid in pentane afforded almost quantitative yields of (with the exception of propyl and hexyl ketone enamines) well-crystallized immonium salts. For these reasons trifluoroacetic acid is probably the best choice for synthetic applications. A well-crystallized immonium salt appears to be a requirement for good yields in the deprotonation reaction. Oily, highly viscous immonium salts were obtained with methyl propyl enamine and trifluoroacetic acid and with methyl isobutyl ketone enamine and methanesulfonic acid. The use of a magnetic stirrer in the deprotonation reaction with these salts gave poor yields which were improved, to some extent, using a highly efficient laminar agitation, see Table 3. The non-crystalline trifluoroacetate from hexyl methyl ketone enamine was less viscous and could be deprotonated with acceptable yields using magnetic stirring.



Scheme 3.

tert-Butylamine is a suitable base due to its low boiling point; any excess is easily removed after the reaction by evaporation. Either a low-boiling petroleum fraction or pentane are preferred solvents.

In order to develop suitable conditions for synthetic application of the deprotonation reaction using one equivalent of base, the influence of the amount of solvent (2 – 5 dm^3/mol of immonium salt), the reaction time (5 – 30 min) and the temperature (0 – 22 °C) were studied using an orthogonal two-level factorial experimental design.[30] It was found that in the experimental domain the temperature is the only variable which influences selectivity and 100 % selectivity is obtained if the temperature is kept below 10 °C.

The 1-isomer can either be generated *in situ* and used directly if the presence of *tert*-butylammonium trifluoroacetate will not disturb subsequent manipulation, or isolated by removal of the precipitated salt and evaporation of the solvent to give a solvent-free enamine with a reproducible ratio 1-isomer – 2-isomer *ca.* 85:15. Recovery of enamines after the protonation – deprotonation – filtration – evaporation sequence were 90 – 97 %. The solvent-free enamine (85 % 1-isomer) did not change the isomer distribution when stored at – 20 °C for 24 h. Evaporation of the solvent causes some isomerisation since ^{1}H NMR spectra on filtered reaction mixtures showed less than 1 % of the 2-isomer.

Extension of the protonation – deprotonation reaction to other enamines. Table 3 lists the results obtained by the deprotonation of several immonium salts. With the exception of benzyl methyl ketone immonium salt the deprotonation reaction gives high yields of the 1-isomer. n-Alkyl methyl ketones show a lower selectivity. The observation that an excess of base gives an increased 1-isomer – 2-isomer ratio might suggest that the rate of isomerisation is higher for these enamines than for those with substituted alkyl groups.

Table 3. Deprotonation of immonium salts from methyl alkyl ketones, RCOMe, in pentane at 0 °C.

Starting ketone R=	Anion	Conditions for deprotonation Base [a]	Equivalents of base	Agitation [b]	Isomer ratio 1-Isomer/ 2-Isomer	Yield [c] %
Propyl	$CF_3CO_2^-$	TBA	1	B	47/53	56
		TBA	5	A	70/30	45
		TBA [d]	1	B	65/35	26
		DIPA	1	A	71/29	29
		DIPA	1	B	70/30	70
		DIPA [e]	1	B	66/34	72
Hexyl	$CF_3CO_2^-$	TBA	1	A	60/40	72
		TBA	5	A	83/17	91
		DIPA	1	A	71/29	82
		DIPA	5	A	80/20	94
		Me_4-pip	1	A	55/45	84
Isobutyl	$CF_3CO_2^-$	TBA	1	A	100/0	100
		DIPA	1	A	100/0	80–90
	$CH_3SO_3^-$	TBA	1	B	100/0	25–32
		DIPA	1	B	100/0	19
Neopentyl	$CF_3CO_2^-$	DIPA	1	A	100/0	100
		N-Me-pip	1	A	100/0	90
2-Phenylethyl	$CF_3CO_2^-$	TBA	1	A	100/0	75
		DIPA	1	A	100/0	77
Benzyl	$CF_3CO_2^-$	TBA	1	A	0/100	90
		DIPA	1	A	0/100	100
Isopropyl [f]	$CF_3CO_2^-$	DIPA	1	A	100/0	100
	Cl^-	DIPA	1	A	100/0	100
Cyclopropyl	$CF_3CO_2^-$	DIPA	1	A	100/0	100
Cyclopentyl	CF_3CO_2	TBA	1	A	100/0	100
		DIPA	1	A	93/7	80
		DIPA	5	A	96/4	85
Cyclohexyl	$CF_3CO_2^-$	TBA	1	A	100/0	90

[a] TBA, *tert*-butylamine; DIPA, diisopropylamine; Me_4-pip, 2,2,6,6-tetramethylpiperidine; *N*-Me-pip, *N*-methylpiperidine. [b] A, magnetic stirring; B, laminar agitation. [c] determined by ^1H NMR with internal standard. [d] −78 °C. [e] −25 °C. [f] from Ref. 13.

EXPERIMEMTAL

^1H NMR spectra were obtained with a Varian EM-360 or a JEOL C-60 HL instrument. ^{13}C NMR spectra were obtained with a JEOL PFT-60 HL or a Varian CFT-20 instrument. Boiling points and melting points are uncorrected. The enamines were prepared from the parent ketone and morpholine by the titanium tetrachloride method.[6] The ketones were commercial products with the exception of cyclopentyl methyl ketone.[31] The amines used were either *puriss* or *p.a.* quality or fractionated prior to use. Ethanol-free chloroform was obtained by shaking commercial *p.a.* chloroform with concentrated sulfuric acid followed by several washings with water, drying with K_2CO_3 and distillation through a Fenske column.

Boiling points and yields of enamines not previously reported are: Enamines from: *hexyl methyl ketone* b.p. 140–141 °C/10 mmHg (72 %), *methyl neopentyl ketone* b.p. 99–101 °C/15 mmHg (51 %), *methyl 2-phenylethyl ketone* b.p. 130 °C/0.3 mmHg (25 %), *benzyl methyl ketone* m.p. 64–66 °C (29 %), *cyclopentyl methyl ketone* b.p. 115–117 °C/10 mmHg (59 %) and *cyclohexyl methyl ketone* b.p. 125–128 °C/10 mmHg (72 %).

Equilibrium composition of the enamines given in Table 1 are the average of 5–10 integrations of the ^1H NMR spectra. The accuracies can be estimated to ±2 %. The samples, *ca.* 100 mg of enamine/0.5 ml of solvent, were stored at room temperature for 20–30 h after the addition of a drop of dilute trifluoroacetic acid prior to recording the spectra.

Preparation of immonium salts for ^{13}C NMR and for deprotonation studies given in Tables 2 and 3. General procedure. To a magnetically stirred solution of 2.0 mmol of the enamine in 6 ml of pentane in a rubber-stoppered centrifuge tube (20 ml) was added dropwise 2.0 ml of a 1.00 M solution of trifluoroacetic acid in pentane. The temperature was maintained at 0 °C during the addition of acid. Subsequent

stirring at room temperature for 30 – 60 min ensured complete formation of the immonium salt which was collected by centrifugation. If solvents other than pentane were used in subsequent steps the remaining pentane was removed in a vacuum desiccator over silica gel and solid paraffin. For the preparation of immonium methanesulfonate ether was employed as solvent using the same procedure as for the trifluoroacetates. Immonium chlorides were obtained by bubbling dry HCl through a solution of 2.0 mmol of enamine in *ca.* 10 ml of pentane at 0 °C. The salts were collected by centrifugation and dried *in vacuo*.

Deprotonation of immonium salts given in Tables 2 and 3. General procedure. To a suspension of 2.0 mmol of immonium salt in 8 ml of pentane at the given temperature was added in one amount 2.0 ml of a 1.00 M solution of the amine base. After stirring for 10 – 30 min a known amount of internal standard was added. ^{1}H NMR samples were withdrawn and the isomer distribution and yields were determined as the average of 5 integrations over well-resolved peaks in the spectrum. The accuracies in yield determination can be estimated to ± 5 % and of isomer distribution to ± 2 %. Benzene was used as internal standard for reactions in pentane. In other solvents triphenylmethane was used.

Preparative scale transformation of an equilibrium mixture of isobutyl methyl ketone – morpholine enamine into the 1-isomer. A typical procedure was: The reaction vessel was a 250 ml three-necked flask fitted with a Hershberg stirrer, a dropping funnel and a drying tube with cotton wool. To 16.9 g (0.10 mol) of an equilibrium mixture of enamine in 80 ml of pentane at 0 °C was added with stirring over 15 min 11.5 g of trifluoroacetic acid in 10 ml of pentane and the mixture stirred for another 20 min. 8.0 g of *tert*-butylamine was then introduced in one amount with vigorous stirring. Stirring was continued for 10 min whereafter the precipitated *tert*-butyl ammonium trifluoroacetate was removed by filtration using a sintered glass funnel. The reaction flask was rinsed with two 10 – 15 ml portions of cooled (0 °C) pentane. Addition of a few crystals of 1,8-bis-dimethylaminonaphthalene ("proton sponge") followed by evaporation under reduced pressure at 0 °C and finally at 1 mmHg afforded 15.9 g of solvent-free enamine, 94 % recovery. The isomer distribution was 1-isomer – 2-isomer, 88:12.

Remarks. Lesser amounts of solvent can be used without loss of selectivity, but the filtration operation is more difficult with concentrated samples. 1,8-Bis-dimethylaminonaphthalene was added prior to evaporation of the solvent to suppress acid-catalyzed isomerisation. Without this precaution the yield of 1-isomer after evaporation was lower, *ca.* 65 %. Use of freeze-drying procedure for removal of the solvent has not been found to improve the isomer ratio.

Attempts at substituting pentane with diethyl ether gave 80 % of 1-isomer after evaporation of the solvent (*ca.* 85 % recovery). One disadvantage in the use of ether is that *tert*-butyl ammonium trifluoroacetate is somewhat soluble and precipitates upon evaporation of the solvent and will therefore contaminate the enamine. Also it is not possible to determine the isomer distribution in ether solution by NMR since the solvent peaks overlap with the enamine signals. However, it seems likely with regard to the purity of the isolated enamine that the reaction in ether is similar to the reaction in pentane.

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