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(26) It is also worth noting that Bell (ref 23) has found a very large Hammett ρ value for the reaction of hydroxide ion with substituted benzaldehydes, counter to the expectation (ref 12) of ρ_{rate}/ρ_{eq} approximately equal to 0.5 for these high barrier reactions.
(27) Jencks (ref 4) has also noted the sensitivity of the thiolate reaction rate constants to variation of the electrophile.
(28) These low β values for thiolate reactions do not appear to occur for concerted reactions, such as S_N2 processes. See, for example: J. M. Wilson, R. J. Bayer, and D. J. Hupe, *J. Am. Chem. Soc.*, **99**, 7922 (1977).
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Hydrolysis of Isomeric Imidate Esters

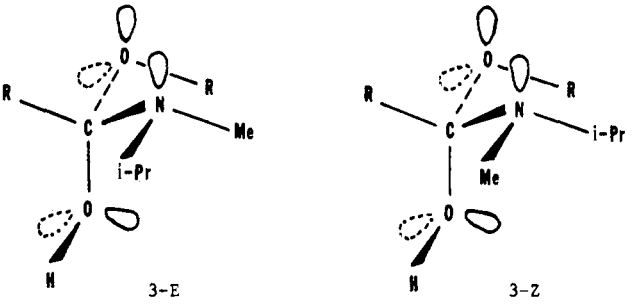
Michael Caswell and Gaston L. Schmir*

Contribution from the Department of Molecular Biophysics and Biochemistry, Yale University School of Medicine, New Haven, Connecticut 06510. *Received June 15, 1979*

Abstract: A study has been made of the hydrolysis of the geometrical isomers of ethyl *N*-methyl-*N*-isopropylacetimidate in aqueous solution at 30 °C (μ = 0.5). The *E* isomer is quantitatively converted to amine and ester in dilute HCl, and to 65% amine at pH >12, with the midpoint of the transition in products at pH 10.2. Hydrolysis of an equimolar mixture of the *E* and *Z* isomers gives the same yield of amine as was obtained from the *E* isomer over the entire pH range. The partial interconversion of the imidate isomers that occurs during hydrolysis at alkaline pH probably proceeds via an enamine intermediate, as shown by the exchange of 33% of the hydrogen of the α-methyl group of the imidate when hydrolysis is carried out in D_2O. Calculations based on the extent of hydrogen–deuterium exchange which accompanies hydrolysis indicate that at least 40% of the imidate undergoes hydrolysis without prior isomerization. It is proposed that the diastereoisomeric intermediates initially formed by hydration of the isomeric imidate esters are rapidly converted to one or more identical tetrahedral intermediates before breaking down to the products of hydrolysis.

The mechanism of the hydrolysis of imidate esters has been intensively studied, owing largely to the relationship of the tetrahedral intermediates formed by hydration of the C=N bond of imidates to the intermediates which occur in acyl transfer reactions such as the aminolysis of esters.[1] A particularly interesting recent development in this field has been the proposal by Deslongchamps and co-workers that the direction of breakdown of such intermediates is under stereoelectronic control.[2] It was suggested that the cleavage of C–N or C–O bonds in the intermediate is greatly assisted by the presence of two nonbonded electron pairs disposed in an antiperiplanar arrangement with respect to the susceptible bond. The energy barrier to such a stereoelectronically favorable bond cleavage was considered to be sufficiently low so that the bond cleavage occurs more rapidly than the rotations of the C–N and C–O single bonds or the nitrogen inversion which are necessary to produce other conformations of the tetrahedral intermediate. As a result, imidates in a conformation which permits breakdown with stereoelectronic assistance are hydrolyzed to yield exclusively amine and ester (at least under conditions where the reaction is under kinetic rather than thermodynamic control), while others give rise to mixtures of amine and amide products.

The postulate that the conformation of an imidate ester is retained in the initially formed tetrahedral intermediate led us to study the hydrolysis of the geometrical isomers of an unsymmetrical N,N-disubstituted imidate salt (Scheme I). Owing to the pyramidal structure of amino nitrogen, stereospecific[2] hydration of the isomeric imidates will produce diastereoisomeric tetrahedral intermediates (**3**-*E* and **3**-*Z*). Nitrogen inversion and rotation about the C–N single bond are required for the interconversion of **3**-*E* and **3**-*Z*. If the products of the hydrolysis of the isomeric imidates **1**-*E* and **1**-*Z* are different, they cannot have arisen from a common intermediate. Such a finding would provide additional support for the view that conformational changes in the tetrahedral intermediate may be slower than the breakdown of the intermediate.[2]



Results

Synthesis. Methylation of ethyl *N*-isopropylacetimidate with methyl fluorosulfonate yielded a 1:1 mixture of the *E* and *Z* isomers of the unsymmetrical *N*-methyl-*N*-isopropyl imidate salt. The pure *E* isomer was obtained after repeated recrystallization of the mixture, but the *Z* isomer could not be purified further. The two products were characterized by elemental analysis, ^{1}H NMR spectra (Figure 1), and quantitative conversion to *N*-methyl-*N*-isopropylamine by hydrolysis in dilute aqueous HCl.

Assignment of the *E* configuration[3] to isomer **1**-*E* is made on the basis of the observed long-range homoallylic coupling of the *N*-methyl resonance at δ 3.10 with the acyl methyl group. The coupling constant $^5J_{trans}$ of ca. 0.9 Hz, which was determined with a 270-MHz spectrometer, is slightly smaller than those of 1.2–1.4 Hz reported for neutral imidate and thioimidate esters,[4] and is in the range of 0.8–1.2 Hz found

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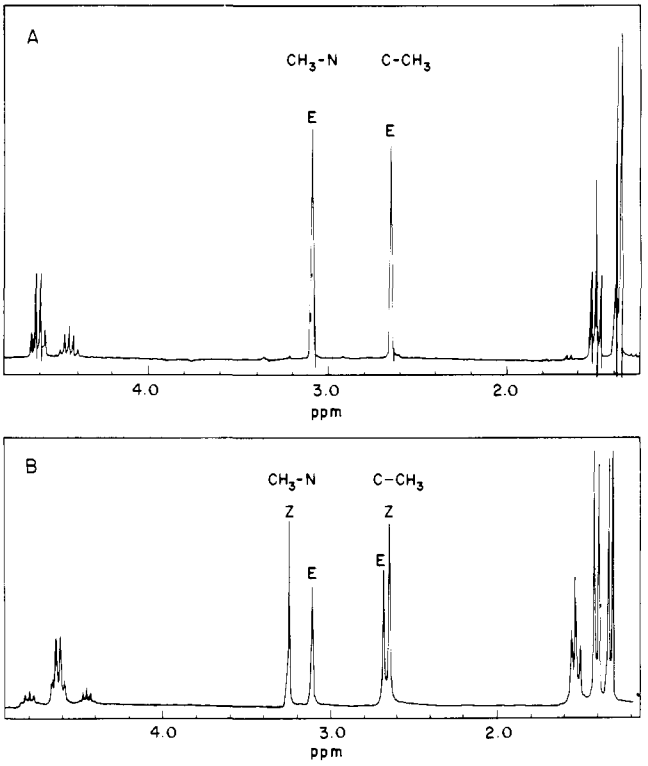
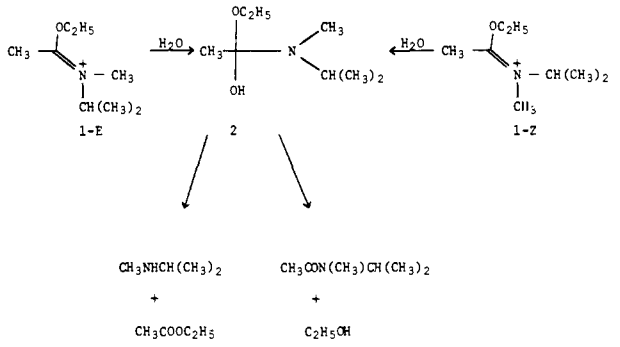


Figure 1. NMR spectra of the geometric isomers of ethyl *N*-methyl-*N*-isopropylacetimidate in $CDCl_3$: A, *E* isomer; B, equimolar mixture of the *E* and *Z* isomers.

Scheme I



with cationic imidates and thioimidates.[4e,5] Although the coupling constant for the *Z* isomer was not determined, it is expected to be ≤ 0.3 Hz.[4,5]

Kinetics of Hydrolysis. In the absence of buffer effects, the hydrolysis of cationic imines (quaternary Schiff bases,[6] thioimidates,[7] and imidates[1d,8,9]) is expected to follow the rate law of eq 1, which results from rate-determining addition of water and hydroxide ion to the iminium group (the change in rate-determining step which occurs at low pH with some Schiff bases and thioimidates is generally not seen in imidate hydrolysis).

$$k_{obsd} = k_w + k_{OH}[OH^-] \quad (1)$$

The rates of the hydrolysis of **1**-*E* and of the equimolar mixture of **1**-*E* and **1**-*Z* were determined in predominantly aqueous solution (30 °C, $\mu = 0.5$) by observing the decrease in UV absorbance at 225 nm. In dilute aqueous HCl (pH 2–3), the hydrolysis of both pure **1**-*E* and of the mixture of isomers accurately follows first-order kinetics (Figure 2B), with a rate constant $k_w = 1.75\ (\pm 0.09) \times 10^{-6}\ s^{-1}$. The linearity of the first-order plot for the isomer mixture suggests that **1**-*E* and **1**-*Z* undergo hydrolysis at essentially equal rates.

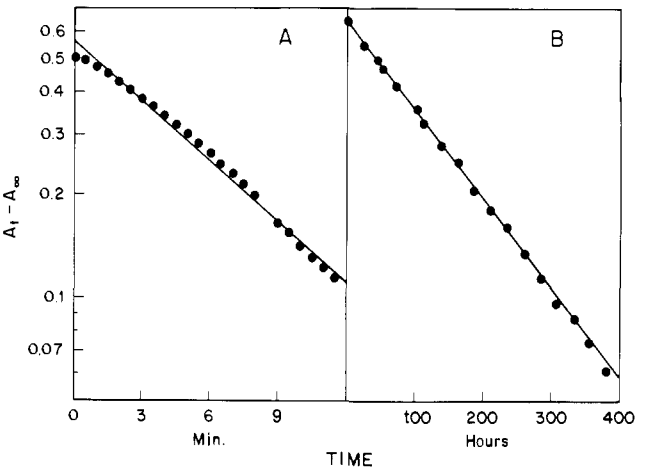


Figure 2. Semilogarithmic plots of the change in absorbance during the hydrolysis of the imidate *E* isomer: A, in 1% acetonitrile–water, 0.025 M borate buffer, pH 8.78; B, 0.01 M HCl.

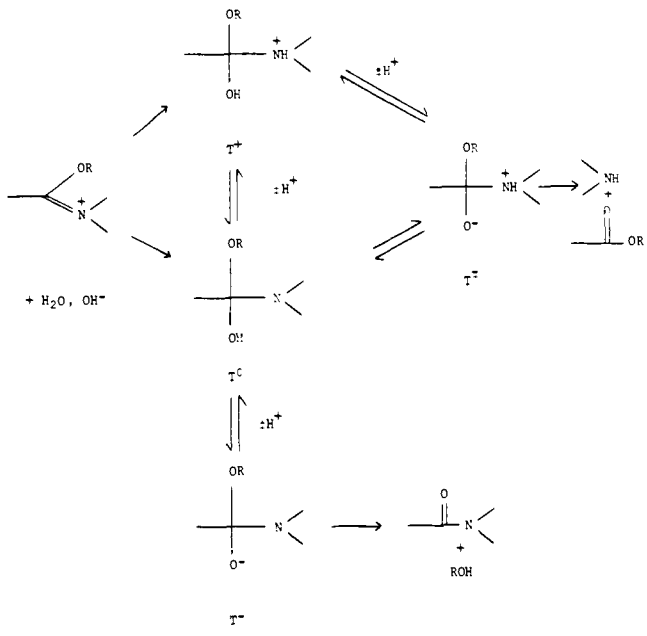
First-order plots for the hydrolysis of the pure *E* isomer at alkaline pH (8.4–9.1) show distinct and reproducible curvature (Figure 2A), although similar experiments with the isomer mixture give acceptably linear plots. As will be shown below, partial conversion of the *E* isomer (ϵ_{225} 580) to the *Z* isomer (ϵ_{225} 720) during alkaline hydrolysis is responsible for the observed deviation from first-order kinetics. Approximate values of $k_{OH} = 260 \pm 30\ M^{-1}\ s^{-1}$ were obtained for the *E* isomer from the straight line which more or less averages the absorbance changes (Figure 2A) and for the isomer mixture. The lack of curvature in the first-order plot for the mixture of **1**-*E* and **1**-*Z* suggests that the *E*:*Z* ratio of one may be near the equilibrium composition and also that the rates of the alkaline hydrolysis of **1**-*E* and **1**-*Z* are similar. Additional rate measurements of the hydrolysis of the isomer mixture at pH 11.75–12.5 (dilute aqueous NaOH) confirmed the above value of k_{OH}. The rate constants k_w and k_{OH} for the reaction of both **1**-*E* and **1**-*Z* with water and hydroxide ion are close to those reported for the hydrolysis of ethyl *N*,*N*-diethylacetimidate.[9,10]

Isomerization. The partial interconversion of the isomeric imidates **1**-*E* and **1**-*Z* concurrent with hydrolysis in alkaline solution was established in two ways.

(a) NMR spectra recorded during the course of the hydrolysis of the pure *E* isomer in D_2O (pD 9.66, 0.025 M borate buffer) revealed the accumulation of the *Z* isomer, up to a maximum concentration of about 20% of the total unreacted imidate. Hydrolysis under similar conditions of the equimolar mixture of the *E* and *Z* isomers showed that the composition of the unreacted imidate changed gradually, with the *E*:*Z* ratio approaching 2:1 in the last stages of the reaction. These observations suggest that the equilibrium constant for the process *Z* isomer $\rightleftharpoons$ *E* isomer in water lies betweeen the limits of 2 and 4. In contrast, the hydrolysis of pure **1**-*E* at pH 2 proceeded without the detectable accumulation of its isomer **1**-*Z*. When the hydrolysis of the isomer mixture at pH 2 was followed by NMR spectroscopy, no change in the isomer ratio was seen. Solutions of the pure *E* imidate or of the isomer mixture in deuterioacetonitrile undergo no change in isomer composition over a period of 10 months.

(b) Hydrolysis of pure **1**-*E* or of the isomer mixture in D_2O at pD 9.7 (0.025 M borate buffer) was accompanied by the incorporation of deuterium in the acetyl group of the ethyl acetate formed in the reaction. Comparison of the area of the acetyl resonance to that of the *N*-methyl group of methylisopropylamine indicated that about 33% of the hydrogen of the acetyl group had undergone exchange. The same amount of

Scheme II



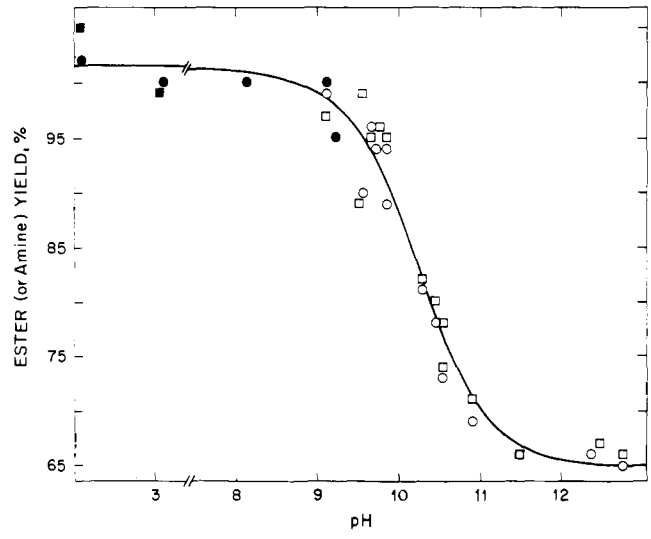


Figure 3. Effect of pH on the yield of methylisopropylamine (closed symbols) or ethyl acetate (open symbols) formed by hydrolysis of the imidate *E* isomer (squares) or of the equimolar mixture of the *E* and *Z* isomer (circles). The line is calculated for the titration of an acid of pK = 10.23, with asymptotes at 101 (low pH) and 65% (high pH).

exchange occurred during hydrolysis at pD 13.2 (NaOD buffer) as measured either by comparison of the α-methyl NMR resonance of ethyl acetate to that of the amine methyl group or from the relative areas of the acetyl and *N*-methyl resonances of *N*-methyl-*N*-isopropylacetamide. Control experiments showed that none of the imidate hydrolysis products underwent exchange of carbon-bound hydrogen under the conditions used for the hydrolysis of **1**-*E* and **1**-*Z*. No incorporation of deuterium took place during the hydrolysis of either pure **1**-*E* or of the mixture of **1**-*E* and **1**-*Z* in 0.01 M DCl solution.

Products of Hydrolysis. The products of the hydrolysis of the *E* imidate and of the equimolar mixture of the *E* and *Z* isomers were determined after at least 6 half-lives of reaction by colorimetric assay for ethyl acetate or methylisopropylamine. Imidates **1**-*E* and **1**-*Z* yield only amine and ester upon hydrolysis in HCl solution. At higher pH, there occurs a decrease in the amine yield, the latter approaching a limit of about 65% at pH >13. The transition in products follows a sigmoid curve with a midpoint at about pH 10.2 (Figure 3). Changing the concentration of borate buffers (0.01–0.03 M) or triethylamine buffers (0.03–0.06 M) had no significant effect on the product distribution.

The computer-calculated nonlinear least-squares fit of the data in Figure 3 to the equation for a sigmoid curve gave the following results for amine or ester yield at low pH , amine or ester yield at high pH , and midpoint of the product transition: *E* isomer, 101%, 65 ± 1%, pH 10.26 ± 0.09; isomer mixture, 101%, 65 ± 1%, pH 10.20 ± 0.07; both data sets combined, 101%, 65 ± 1%, pH 10.23 ± 0.06. There appears to be no difference in the product distribution obtained from hydrolysis of the pure *E* isomer or of an equimolar mixture of the *E* and *Z* isomers of ethyl *N*-isopropyl-*N*-methylacetimidate.

Discussion

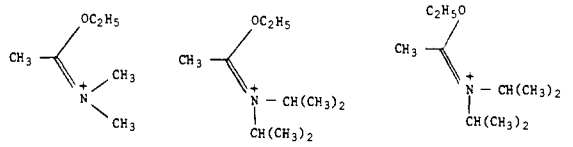
The overall mechanism of the hydrolysis of imidate esters which has emerged in recent years is outlined in Scheme II. Although it is generally agreed that the rate-determining step usually consists of the reaction of a cationic imidate with water or hydroxide ion to form a cationic (T^+) or neutral (T^0) tetrahedral addition intermediate, the pathways which lead from intermediate to products are complex and depend on the structure of the imidate.[1c,d,9,11,12] Thus, the four possible intermediate species (T^+, T^0, $T^\pm$, and T^-) may or may not be at equilibrium with respect to proton transport, as shown by the existence of kinetically important buffer-catalyzed protonation steps.[1d,7c,13] In some instances, some of the possible intermediates are believed to be too unstable to exist, so that the cleavage of C–O or C–N bonds may be concerted with proton donation or abstraction.[11]

Prior to the studies of Deslongchamps and co-workers,[2] the observed differences in the direction of breakdown of the several species of the tetrahedral intermediate were explained mainly in terms of relative leaving abilities of amines and alcohols. The principal factors were considered to be the pK_a of the conjugate acid of the leaving group, the nature of the departing atom (oxygen or nitrogen), and the availability of protons which could be used to enhance the leaving ability of a given group. The ability of the remaining heteroatoms to stabilize the incipient carbonium ion center was also thought to be important. In general (though there were some notable exceptions in the case of imidates derived from very weakly basic amines[1c] or from phenols[1d]) cationic and neutral intermediates were found to expel mainly amine, while anionic intermediates broke down principally to amide and alcohol.

To explain the observation that certain cyclic and acyclic imidate esters give high yields of amine, sometimes as high as 100%, upon hydrolysis at alkaline pH (where the hydrolysis products arise probably from T^-), Deslongchamps et al.[2] proposed that the conformation of the imidate has an important influence on the nature of the hydrolysis products. This conformation, determined by the steric properties of the substituent groups on the OC=N system of the imidate, was considered to be conserved in the initially formed tetrahedral intermediate. In favorable situations, when stereoelectronic assistance to the breakdown of the intermediate is possible, expulsion of the amine occurs more rapidly than other conformations of the intermediate can be produced. When favorable stereoelectronic factors are not present in the initially formed tetrahedral intermediates, bond rotations or nitrogen inversion leads to other conformations. The products of the decomposition of these new conformations of the intermediate generally consist of mixtures of amine (C–N bond cleavage) and amide (C–O bond cleavage).

The hydrolysis of ethyl *N*,*N*-dimethylacetimidate (**4**) at about pH 13 results in the formation of dimethylamine in ca. 80% yield, while the corresponding *N*,*N*-diisopropyl imidate

(**5**) produces amine in a yield of only 6%.[2d,9] In terms of the stereoelectronic theory, severe steric interactions between the *O*-ethyl and the proximal *N*-isopropyl group in the conformation **5a** compel the imidate to adopt conformation **5b.** This



4 5a 5b

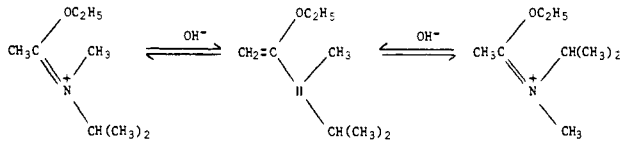
conformation is retained in the initially formed tetrahedral intermediate and is not suitable for orbital-assisted cleavage of the C–N bond. The ensuing conformational changes produce one or more intermediates which decompose mainly by expulsion of alcohol. The less demanding steric requirements of the *N*-methyl group proximal to the ethoxy group of **4** allow the imidate to exist in part in the configuration shown which, after hydration, leads to the immediate expulsion of amine. According to the theory, the important point is that the steric interactions present in the imidate are retained in the tetrahedral intermediate and thus influence the nature of the hydrolysis products.

If imidate conformation controls the choice of hydrolytic pathway, it seems reasonable to assume that the geometrical isomers **1**-*E* and **1**-*Z* of ethyl *N*-methyl-*N*-isopropylacetimidate will retain in large part the essential steric interactions which determined the different courses of hydrolyses of the imidates **4** and **5**. The *Z* isomer may be considered analogous to the diisopropyl imidate **5b** in that it should prefer a conformation which avoids the unfavorable steric interaction of the *O*-ethyl group and the *N*-isopropyl substituent. Likewise, the conformation of the *E* isomer with regard to the *O*-ethyl and *N*-methyl substituents should reflect that of the dimethyl imidate **4**. It follows that the products of the hydrolysis of **1**-*E* may be expected to resemble those of **4** (high amine yield) while **1**-*Z* should be converted mainly to amide and alcohol, if the different steric characteristics of **1**-*E* and **1**-*Z* are transmitted to the derived tetrahedral intermediates and persist throughout the course of the hydrolysis.

The tetrahedral intermediates **3**-*E* and **3**-*Z* formed by hydration of the isomeric imidates **1**-*E* and **1**-*Z* differ in one important way from other tetrahedral intermediates whose patterns of breakdown have been compared, in that they can be interconverted to identical structures via relatively facile processes (nitrogen inversion and rotation about single bonds). If interconversion of **3**-*E* and **3**-*Z* is rapid relative to the rate of breakdown of the intermediates, the hydrolysis of the isomeric imidates **1**-*E* and **1**-*Z* should give rise to identical products. The same results will be obtained if interconversion of the geometrical isomers **1**-*E* and **1**-*Z* is faster than the addition of water or hydroxide ion to the imidate. The observation (Figure 3) that the products of hydrolysis of the pure *E* isomer are indistinguishable from those of the mixture of *E* and *Z* isomers suggests that the stereochemical integrity of **1**-*E* and **1**-*Z* has been lost, *either at the imidate or at the tetrahedral intermediate level.*

The interconversion of the *E* and *Z* isomers of imidate and thioimidate esters has received recent attention, and several possible mechanisms have been considered for this reaction. Imidate and thioimidate free bases are generally believed to undergo isomerization via a planar inversion process,[4c,d,14,15] and in some instances via an imine–enamine pathway.[4d] Protonated imidates and thioimidates may undergo rotation about the C–N double bond in strongly acidic solvents;[5,15] in neutral or basic media, isomerization may also occur via the enamine or through a deprotonation–inversion–reprotonation mechanism.[5,14] Wide differences exist in the rate of isomerization of protonated imidates. For example, protonated methyl *N*-

Scheme III



methylacetimidate requires prolonged heating (90 h) at 80 °C to achieve equilibrium between *E* and *Z* forms,[16] and the rate of isomerization of protonated methyl *N*-methylbenzimidate is extremely slow.[15] In contrast, the half-time for the isomerization of methyl *N*-phenylbenzimidate at 0 °C in trifluoroacetic acid is of the order of 1–2 h.[15] Scant information is available concerning the isomerization of cationic imidates derived from secondary amines. For the few examples which have been described, isomerization in acidic solvents (trifluoro- or dichloroacetic acid) or in acetonitrile is thought to proceed by rotation about the double bond.[5,17] In one instance of isomerization in aqueous HCl, a mechanism involving reversible addition of water to the C=N bond has been proposed.[2f,30] As with protonated imidates derived from methylamine, the cationic imidate methyl *N,N*-dimethylformimidate appears not to undergo uncatalyzed isomerization even at elevated temperature (in this case, of course, the isomerization process is a virtual reaction, the occurrence of which would lead to coalescence of the two separate NCH_3 signals in the NMR spectrum).[18]

The isomeric imidates **1**-*E* and **1**-*Z* do not undergo interconversion in dilute aqueous HCl (30 °C) even after many days. This behavior is consistent with that of protonated or *N,N*-dialkyl imidates derived from simple aliphatic primary or secondary amines. The probable mechanism for the isomerization that occurs in alkaline solution (see Results) is outlined in Scheme III. Base-catalyzed proton abstraction from the α-methyl group of the imidate gives rise to the enamine; the latter is converted to a mixture of the *E* and *Z* imidates by reprotonation on carbon. This mechanism accounts for the introduction of deuterium in the corresponding methyl groups of the hydrolysis products, when the hydrolysis is carried out in D_2O. A similar explanation was offered for the incorporation of solvent deuterium in the products of the alkaline hydrolysis of ethyl *N,N*-dimethylthioacetimidate,[7b] where 62% of the α-methyl protons were exchanged for deuterium, and of *p*-cresyl *N*-methylacetimidate.[14]

The conclusion that thermodynamic equilibrium between the imidate isomers **1**-*E* and **1**-*Z* is not achieved during the course of the hydrolysis is supported by the following observations: (a) even after more than 80% of hydrolysis, the composition of the mixture of *E* and *Z* isomers formed from pure *E* isomer never equals the composition of the isomer mixture that is present in the late stages of the hydrolysis of the initially 1:1 *E*:*Z* mixtures; (b) only about 33% of the α-methyl protons available for exchange are replaced by deuterium when the imidate hydrolysis is carried out in D_2O.

For the purposes of the present study, it is important to determine what fraction of the imidate esters (pure *E* or the isomer mixture) underwent hydrolysis prior to any isomerization. The competing hydrolysis and isomerization reactions are represented in Scheme V (Appendix), where A_0, A_1, A_2, A_3 are respectively undeuterated, monodeuterio-, dideuterio-, and trideuterioimidate. The symbols A_4, A_5, A_6, and A_7 stand for the undeuterated and mono-, di-, and trideuterated hydrolysis products formed from the corresponding imidate esters. The following assumptions were made in this analysis: (a) The rates of hydrolysis of the *E* and *Z* isomers are equal, as are the rates of proton abstraction; the first assumption is supported by the kinetic data obtained (Results), while the finding that both the pure *E* isomer and the 1:1 isomer mixture in-

corporate deuterium to the same extent is evidence for the second. (b) Secondary deuterium isotope effects on hydrolysis and enamine formation are expected to be small and may be neglected.[7b] (c) Owing to the very low concentration of H_2O and HOD, the isomerization steps are essentially irreversible. The coefficients 2/3 and 1/3 applied to the second and third isomerization steps are statistical factors which take into account the diminishing number of hydrogen atoms in A_1 and A_2.

From the observed 33% deuterium incorporation, the ratio of the rate of hydrolysis to the rate of exchange (k_2/k_1) is calculated to be 0.67, from which it follows that A_4/A_0^0 = 0.40, i.e., 40% of the imidate ester present at zero time undergoes hydrolysis without any exchange (see Appendix). Since some of the imidate will undergo deuterium exchange *without* isomerization, the value of 40% represents the minimum amount of hydrolysis prior to isomerization. Use of the *N,N*-dimethyl imidate (**4**) and the *N,N*-diisopropyl imidate (**5**) as models for **1**-*E* and **1**-*Z*, respectively, leads to the conclusion that a difference of 15% in amine yield should be found when the products of the hydrolysis at high pH of the pure *E* isomer are compared to those of the 1:1 isomer mixture.[31] The identity over the entire pH range of the curves which relate percent amine yield to pH (Figure 3) suggests that, regardless of their origin, the anionic intermediates (T^-) formed from the *E* and *Z* imidates both break down to amine in about 65% yield, the neutral intermediates (T^0 or $T^{\pm}$) are quantitatively converted to amine, and the relative rates of breakdown of neutral and anionic intermediates are the same for both isomers (this rate ratio determines the pH value at which the inflection point of the sigmoid product vs. pH curve occurs). The simplest explanation which accommodates these findings is that the diastereoisomeric intermediates **3**-*E* and **3**-*Z* initially formed by hydration of the isomeric imidates are rapidly interconverted prior to breakdown, and that the products of the hydrolysis of the *E* and *Z* imidates arise from one or more identical tetrahedral intermediates.

The appreciable interconversion of the *E* and *Z* imidates and the fact that the *Z* isomer was not obtained in a pure state make it difficult to arrive at completely definitive conclusions. For example, if it is assumed that a 5% difference in amine yield from hydrolysis of the pure *E* isomer as compared to hydrolysis of the isomer mixture might have been missed, it can be calculated that a difference in amine yield of 25% or less between pure *E* and pure *Z* isomers cannot be ruled out. Nevertheless, the fact that the isomeric imidate esters certainly do not reach equilibrium during the course of the hydrolysis, and that the products of hydrolysis appear to be identical, suggests that a mechanism involving rapidly equilibrating intermediates is probably, though not conclusively, correct. A recent study of the alkaline hydrolysis of isomeric formimidate esters has led to similar conclusions.[30]

Experimental Section[19]

***N*-Isopropylacetamide**[20] had bp 78 °C (2.5 mm) (lit.[20] 74–75 °C (1.5 mm)).

***N*-Methyl-*N*-isopropylacetamide** was synthesized from methylisopropylamine (Pfaltz and Bauer) and acetyl chloride by a procedure similar to that used for *N*-isopropylacetamide: yield 62%; bp 67 °C (17 mm) (lit.[21] 60 °C (17 mm)); IR (neat) 6.11 μ (C=O); NMR ($CDCl_3$) δ 1.14 (d, 6 H, $CH(CH_3)_2$), 2.06 (s, 1.5, CCH_3), 2.11 (s, 1.5, CCH_3), 2.79 (s, 1.5, NCH_3), 2.82 (s, 1.5, NCH_3), 4.06 (m, 0.5, $CH(CH_3)_2$), 4.91 (m, 0.5, $CH(CH_3)_2$). The appearance of two resonances for the NCH_3, CCH_3, and $NCH(CH_3)_2$ groups reflects the presence of two isomers owing to restricted rotation about the amide bond.[22]

Methylisopropyl[α-(ethoxy)ethylidene]ammonium Fluorosulfonate. A. Ethyl *N*-Isopropylacetimidate. To a solution of 77.5 g (0.41 mol) of triethyloxonium tetrafluoroborate[23] in 200 mL of dry CH_2Cl_2 chilled to 0 °C was added dropwise with the exclusion of moisture a solution of 41.25 g (0.41 mol) of *N*-isopropylacetamide in 100 mL of dry CH_2Cl_2. The mixture was allowed to warm to room temperature as stirring continued for an additional 1 h. After removal of the solvent, the imidate was neutralized at 0 °C by a solution of 24 g of KOH in a minimum amount of saturated aqueous NaCl. The product was extracted into four portions of ether which in turn was washed four times with saturated aqueous NaCl. The ethereal phase, after drying over $MgSO_4$, was distilled at atmospheric pressure: yield 20.2 g (38%); bp 123–125 °C; IR (neat) 5.94 μ (C=N); NMR ($CDCl_3$) δ 1.02 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 1.16 (t, J = 7 Hz, 3, CH_2CH_3), 1.83 (s, 3, CCH_3), 3.44 (m, J = 6 Hz, 1, $CH(CH_3)_2$), 4.00 (q, J = 7 Hz, 2, CH_2CH_3).

Anal. Calcd for $C_7H_{15}NO$ (129.29): C, 65.07; H, 11.70; N, 10.48. Found: C, 65.30; H, 11.49; N, 10.47.

B. To a solution of 8.5 g (66 mmol) of ethyl *N*-isopropylacetimidate in 40 mL of CH_2Cl_2 at 0 °C was added dropwise a solution of 5.84 mL (72 mmol) of methyl fluorosulfonate in 15 mL of CH_2Cl_2. The mixture was stirred for 1 h at 0 °C and then allowed to warm to room temperature. After 0.5 h the solvent was removed, and the residue was crystallized from ethanol–ether, affording a mixture of 50% *E* isomer and 50% *Z* isomer as calculated from the relative areas of the NCH_3 resonances in the NMR spectrum: yield 11.5 g (72%); mp 82–83 °C; IR (Nujol) 6.07 μ (C=N$^+$); UV (H_2O) ϵ_{225} 655; NMR ($CDCl_3$) δ 1.32 (d, J = 7 Hz, 3 H, *Z* $CH(CH_3)_2$), 1.40 (d, J = 8 Hz, 3, *E* $CH(CH_3)_2$), 1.53 (t, J = 7 Hz, 3, CH_2CH_3), 2.65 (s, 1.5, *E* CCH_3), 2.68 (s, 1.5, *Z* CCH_3), 3.10 (s, 1.5, *E* NCH_3), 3.24 (s, 1.5, *Z* NCH_3), 4.46 (m, J = 6 Hz, 0.5, *E* $CH(CH_3)_2$), 4.64 (q, J = 8 Hz, 2, CH_2CH_3), 4.81 (m, J = 7 Hz, 0.5, *Z* $CH(CH_3)_2$).

Anal. Calcd for $C_8H_{18}FNO_4S$ (243.30): C, 39.49; H, 7.46; N, 5.76. Found: C, 39.37; H, 7.41; N, 5.71.

The mixture of isomers was dissolved in a minimum amount of acetonitrile at room temperature. Ether was added just to the point of cloudiness and the solution was chilled at 4 °C for 1–2 h. Three recrystallizations were required to obtain pure *E* isomer: yield 35%; mp 78–80 °C; IR (Nujol) 6.09 μ (C=N$^+$); UV (H_2O) ϵ_{225} 580; NMR ($CDCl_3$) δ 1.37 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$), 1.50 (t, J = 7 Hz, 3, CH_2CH_3), 2.65 (s, 3, CCH_3), 3.09 (s, J = 0.9 Hz, 3, NCH_3), 4.44 (m, J = 7 Hz, 1, $CH(CH_3)_2$), 4.62 (q, J = 7 Hz, 2, CH_2CH_3).

Anal. Calcd for $C_8H_{18}FNO_4S$ (243.30): C, 39.49; H, 7.46; N, 5.76. Found: C, 39.58; H, 7.58; N, 5.85.

Methylisopropylammonium *p*-toluenesulfonate was prepared by adding 1.0 g of methylisopropylamine to a solution of 2.6 g of *p*-toluenesulfonic acid in 10 mL of ethanol. The product obtained after addition of ether was recrystallized twice from ethanol–ether and had mp 71.0–71.4 °C.

Anal. Calcd for $C_{11}H_{19}NO_3S$ (245.34): C, 53.85; H, 7.81; N, 5.71; O, 19.56. Found: C, 53.88; H, 7.79; N, 5.79; O, 19.73.

Kinetics. Deionized, glass-distilled, freshly boiled water was used for all solutions. Reactions were carried out at 30 °C at an ionic strength of 0.5 maintained with KCl. Buffers were hydrogen chloride, sodium borate (0.01–0.05 M), and sodium hydroxide. At acidic pH, the aqueous reaction mixture was sealed in glass ampules which were immersed in a constant-temperature bath. The decrease in absorbance of the reaction mixture at 225 nm was measured with a Zeiss PMQ II or Gilford 240 spectrophotometer. With sodium borate buffer (pH 8.5–9.1), hydrolysis was initiated by adding 0.030 mL of a 0.1 M solution of the imidate in acetonitrile to 3.00 mL of the buffer solution, equilibrated at 30 °C in the jacketed cell holder of a Cary 15 spectrophotometer. At pH greater than 11.7, hydrolysis of the imidate was followed with a Durrum-Gibson D-110 stopped-flow spectrophotometer. The reaction was initiated by mixing the aqueous imidate solution (0.004 M) with an equal volume of sodium hydroxide buffer. Despite the very low rate of hydrolysis at low pH ($t_{1/2}$ ca. 110 h), all reactions were followed to completion and rate constants were calculated from the slopes of semilogarithmic plots of absorbance changes vs. time, using a linear least-squares program. Second-order rate constants were based on the activity of hydroxide ion which was calculated from the pH meter reading and pK_w = 13.83.[24] For reactions in D_2O, pD was obtained from the expression pD = pH meter reading + 0.41.[25] At greater than 0.015 M deuteroxide, pD values were obtained by extrapolation of the linear dependence of log [OD^-] vs. pD, which was determined with deuteroxide solutions in the concentration range 0.0016–0.014 M NaOD.

Product Analysis. The extent of C–N bond cleavage in the hydrolysis of the imidates was determined by assay for methylisopro-

pylamine or ethyl acetate after more than 10 half-lives of reaction. Reaction mixtures usually contained imidate at 10^{-4} M when the amine assay was used and at 3×10^{-4} M when ethyl acetate formation was measured. The concentration of amine was determined colorimetrically by the procedure described for dimethylamine.[26] A 1.0-mL sample of methylisopropylamine, added as the *p*-toluenesulfonate, at 1×10^{-4} M gave an absorbance of 0.40 unit at 540 nm. The yield of ethyl acetate was determined by the hydroxamic acid method previously described for methyl acetate.[27] A 2.0-mL sample of ethyl acetate at 3×10^{-4} M resulted in an absorbance of 0.60 unit when cells with a 5-cm path length were used. For HCl or NaOH (NaOD) buffers the solvent was pure water, while for borate buffer (0.01–0.02 M between pH 8.13 and 9.86) and triethylamine buffer (0.03–0.06 M between pH 10.28 and 11.48) the solvent was 0.7% (v/v) acetonitrile–water.

To avoid the alkaline hydrolysis of ethyl acetate for reactions at pH greater than 10.6, a rapid quench technique, using a Durrum D-133 multimixing system, was employed. The aqueous imidate solution was mixed with the alkaline buffer and the reaction was allowed to proceed for a time of about 10–20 half-lives of imidate hydrolysis before being stopped by addition of an equal volume of aqueous HCl. The approximate[28] second-order rate constant for the alkaline hydrolysis of ethyl acetate at 30 °C (0.17 M^{-1} s^{-1}) is ~1500 times smaller than that for hydrolysis of the imidate, so that less than 1% of the ethyl acetate produced will have been hydrolyzed after 20 half-lives of imidate hydrolysis. For example, aqueous imidate was mixed with 0.06 M triethylamine buffer at pH 11.48 ($t_{1/2}$ = 0.6 s for imidate hydrolysis), and after a preset delay of 5 or 10 s the mixture was added to an equal volume of 0.015 M HCl, the final pH being about 4. This solution was assayed for ethyl acetate. When a 5-s delay was used before quenching, the extent of C–N bond cleavage was found to be 68 and 65% for two separate determinations. After a 10-s delay, the ester yield was found to be 67 and 65%. The observed ester yield was never affected by increasing the delay time from 10 to 20 half-lives of imidate hydrolysis. At pH 10.53, there was no difference between the results obtained by using the multimixing system and those obtained by using a vortex mixer.

NMR Studies. The products of imidate hydrolysis in D_2O were identified by their NMR spectrum. For hydrolysis of the *E* isomer at pD <9.8, methylisopropylamine (δ 2.69, NCH_3) and ethyl acetate (δ 2.07, CCH_3) resonances were seen, but amide resonances were absent. At pD 13.23 and 13.59, the NMR spectrum of the products could be accounted for in terms of C–O and C–N bond cleavage of the imidate.

Experiments designed to demonstrate the isomerization of **1**-*E* and **1**-*Z* during alkaline hydrolysis were carried out in D_2O at the probe temperature (35 °C with the Varian T-60 and 19 °C with the Bruker spectrometer), and imidate concentrations were 0.1 and 0.03 M, respectively. For the determination of the extent of deuterium incorporation in the α-methyl group of the imidates during alkaline hydrolysis, reactions were performed in D_2O at 30 °C, with the imidate at a final concentration of 0.002 M. After completion of reaction (with rapid quenching if necessary), integrated NMR spectra were obtained with the 270-MHz Bruker spectrometer.

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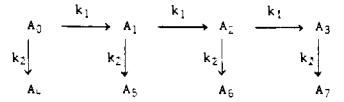
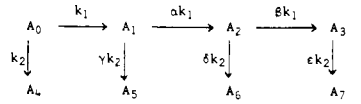
Appendix

The mathematical methods described by Rodiguin and Rodiguina[29] were used to derive the equations which permit the calculation of the fraction of imidate ester which undergoes hydrolysis without prior isomerization. Consider Scheme IV where A_0, A_1, A_2, and A_3 represent undeuterated, monodeuterated, dideuterated, and trideuterated imidate, respectively, and A_4, A_5, A_6, and A_7 are the corresponding products of hydrolysis. The rate constants k_1 and k_2 are for deuterium incorporation and hydrolysis, respectively. The equations which convert the transforms for A_4, A_5, and A_6 to their originals are

Scheme IV



Scheme V



known,[29] but that for A_7 does not seem to have been reported. However, the mole fraction of A_7 present at infinite time is readily obtained from the equation

$$A_7 = A_0^0 - A_4 - A_5 - A_6$$

where A_0^0 is the total imidate present at zero time. The following equations give the amounts of the four possible products present at infinite time.

$$A_4 = k_2A_0^0/(k_1 + k_2) \qquad A_5 = \frac{k_1k_2A_0^0}{(k_1 + k_2)^2}$$

$$A_6 = k_1^2k_2A_0^0/(k_1 + k_2)^3 \qquad A_7 = \frac{k_1^3A_0^0}{(k_1 + k_2)^3}$$

The fraction (f^d) of the hydrogen atoms initially present in the α-methyl group of the imidate which have been replaced by deuterium at infinite time is related to the ratio a of the rate constants k_1 and k_2 as follows.

$$f^d = \frac{A_5 + 2A_6 + 3A_7}{3A_0^0}$$

$$f^d = \frac{k_1^3 + k_1^2k_2 + k_1k_2^2/3}{(k_1 + k_2)^3}$$

Let $a = k_2/k_1$

$$f^d = \frac{1 + a + a^2/3}{(1 + a)^3}$$

$$\frac{A_4}{A_0^0} = \frac{a}{1 + a} = \frac{k_2}{k_1 + k_2}$$

Solving the cubic equation for a allows the calculation of the desired ratio A_4/A_0^0.

Scheme V represents a generalized version of Scheme IV and allows the inclusion of coefficients which modify k_1 and k_2, such as might result from secondary deuterium isotope effects, for example. Treatment of this scheme by the method used above gives the following results.

$$A_4 = \frac{k_2A_0^0}{k_1 + k_2} \qquad A_5 = \frac{\gamma k_2k_1A_0^0}{(k_1 + k_2)(\gamma k_2 + \alpha k_1)}$$

$$A_6 = \frac{\alpha\delta k_2k_1^2A_0^0}{(k_1 + k_2)(\gamma k_2 + \alpha k_1)(\beta k_1 + \delta k_2)}$$

$$A_7 = \frac{\alpha\beta k_1^3A_0^0}{(k_1 + k_2)(\gamma k_2 + \alpha k_1)(\beta k_1 + \delta k_2)}$$

$$f^d = \frac{\gamma\delta k_1k_2^2/3 + (\beta\gamma/3 + 2\alpha\delta/3)k_1^2k_2 + \alpha\beta k_1^3}{(k_1 + k_2)(\alpha k_1 + \gamma k_2)(\beta k_1 + \delta k_2)}$$

In the present study, it is assumed that secondary deuterium isotope effects may be neglected. When statistical correction factors are included (α = 2/3 and β = 1/3; γ, δ, and ϵ = 1), the expression for f^d becomes

$$f^d = \frac{k_1k_2^2/3 + 5k_1^2k_2/9 + 2k_1^3/9}{(k_1 + k_2)(2k_1/3 + k_2)(k_1/3 + k_2)}$$

$$f^d = \frac{3a^2 + 5a + 2}{9a^3 + 18a^2 + 11a + 2}$$

Using the experimentally determined value $f^d = 0.33$ leads to $a = k_2/k_1 = 0.67$ and $A_4/A_0^0 = 0.40$.

It should be noted that the value calculated for A_4/A_0^0 is not highly sensitive to the values used for the coefficients in Scheme V. For example, if statistical corrections are omitted (as in Scheme IV) and f^d is again taken as 0.33, $A_4/A_0^0 = 0.46$.

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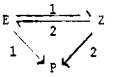
(31) A referee has suggested that scheme i, with relative values of the rate constants as shown, satisfactorily describes the changes in isomer composition observed during hydrolysis at alkaline pH. Although we cannot at present unequivocally rule out this scheme, it should be noted that the principal conclusions of this study remain unchanged, regardless of which kinetic scheme is used to calculate the predicted difference in amine yield. The integrated rate equations for scheme i are readily derived,[29] and lead to the following conclusions: (a) starting with the pure **1**-*E* isomer, 67% of the hydrolysis product comes from **1**-*E* and 33% from **1**-*Z*; (b) starting with the equimolar mixture of **1**-*E* and **1**-*Z*, 50% of the product comes from each isomer. Using again the imidates **4** and **5** as models for **1**-*E* and **1**-*Z*, respectively, a difference of 13% in amine yield is predicted.



i

On the Mechanism of the Keto–Enol Tautomerism in Radical Cations and Gas-Phase Closed-Shell Systems

Janet S. Splitter* and Melvin Calvin

Contribution from the Laboratory of Chemical Biodynamics and Department of Chemistry, University of California, Berkeley, California 94720. *Received February 13, 1979*

Abstract: The enol-keto tautomerism in radical cations has been considered to involve a symmetry-forbidden 1,3-hydrogen shift. An alternative process involves two consecutive 1,2-hydrogen shifts. The ΔH_f's of the intermediate ions formed by a 1,2-hydrogen shift in the radical cations of phenol and the enol form of acetic acid have been calculated to be 220 and 191 kcal/mol, respectively. These ΔH_f's indicate barriers to the keto-enol tautomerism via two consecutive 1,2-hydrogen shifts of 50 and 47 kcal/mol, respectively, in good agreement with previously determined experimental values of 55 and 51 ± 10 kcal/mol, respectively. The tautomerism in the closed-shell systems 1-butene ⇌ 2-butene, vinyl alcohol ⇌ acetaldehyde, $H_2C{=}O^+CH_3$ ⇌ $H_3CO^+{=}CH_2$, and $CH_3CH{=}O^+CH_3$ ⇌ $CH_3CH_2O^+{=}CH_2$ is discussed in terms of two consecutive 1,2-hydrogen shifts.

Recently, a maximum barrier of 2.4 eV (55.2 kcal/mol) was determined[1] for the enol-keto tautomerism of the metastable phenol radical cation (**1**)[2] to the 2,4-cyclohexadien-1-one radical cation (**3**).[5] This tautomerism was considered to be a specific example of a sigmatropic 1,3-hydrogen migration, a symmetry-forbidden process.[1]

We propose that the energetics of this reaction may be accounted for by two consecutive 1,2-hydrogen shifts.[9] The first 1,2-hydrogen shift would give ion **2**, which should approximate the structure of the intermediate ion in the enol-keto tautomerism by this mechanism.[10,14] The formation of ion **2** would be in accord with the "tight" transition state indicated by the large kinetic shift observed in the decomposition of **1** to give the M − CO ion.[1] The kinetic shift was manifested in a large variation of kinetic energy release with decomposition time.[1]

Energy Estimates and Reaction Mechanism. The ΔH_f of ion **2** may be estimated from the proton affinity of benzene,[16]

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