93 °C (lit.[2,31] mp 93 °C); 8, mp 143 °C (lit.[2,32] mp 143 °C). Methanol and methanolic potassium methoxide solutions were prepared as previously described.[14] The various buffers used for the rate measurements were purified according to classical methods.

Rate and pH Measurements. Stopped-flow determinations were performed on a Durrum stopped-flow spectrophotometer, the cell compartment of which was maintained to ±0.5 °C. Other kinetic measurements were made by using a Beckman Acta III spectrophotometer. All kinetic runs were carried out under pseudo-first-order conditions with a substrate concentration in the range 5×10^{-5}–10^{-4} M. Rate constants are accurate to ±3%. The ionic strength of the potassium methoxide solutions with $[CH_3O^-] < 10^{-2}$ M was kept constant at 0.01 M by adding KBr as necessary.

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The pH of buffered solutions at 20 °C was measured according to a method previously reported by using an hydrogen electrode.[14] The pH values so obtained are relative to the standard state in methanol. The $[CH_3O^-]$ concentration of these solutions (I = 0.01 M) was calculated by solving eq 8 where K_s is the autoprotolysis

$$[CH_3O^-] = K_s/a_{H^+}\gamma_{\pm} \quad (8)$$

constant and $\gamma_{\pm}$ the mean activity coefficient at I = 0.01 M ($K_s = 10^{-16.86}$; $\gamma_{\pm}$ = 0.66 at t = 20 °C).[14]

Registry No. **5**, 16322-19-3; **6**, 73466-75-8; **7**, 59344-28-4; **8**, 18771-85-2; **9**, 59344-30-8; **10**, 59344-31-9, 865-33-8.

Supplementary Material Available: Figures 2, 3, and 6 showing the plots of k_2^{obsd}, k_1^{obsd}, and $k_2'^{obsd}(1 + K_1[CH_3O^-])$, respectively, vs. the methoxide ion concentration for the appearance of the adducts **9** or **10** (3 pages). Ordering information is given on any current masthead page.

Carbon-13 and Proton Nuclear Magnetic Resonance Chemical Shift Assignments in Imides and β-Diketone Enolates[1]

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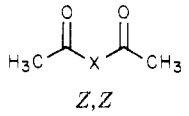
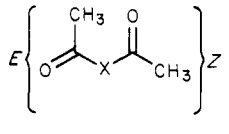
The low-temperature ^1H and ^{13}C NMR spectra of the imides diacetamide and *N*-acetylpropionamide and the enolate anions 2,4-pentanedionate (acetylacetonate) and 2,4-hexanedionate (propionylacetonate) are presented. Under the conditions used, torsion about C–N and C–C partial double bonds is slow on the NMR time scale, and in the symmetrical compounds three different kinds of acetyl methyl and acetyl carbonyl (in ^{13}C NMR spectra) resonances can be observed: the single resonances from *Z,Z* diastereomers and pairs of resonances from diastereotopic acetyl groups in the *E,Z* (and *Z,E*) diastereomers. The spectra of the unsymmetrical compounds which have two diastereomeric forms (*E,Z* and *Z,E*) were used to complete chemical shift assignments for the diastereotopic groups in the symmetrical compounds which have only a single *E,Z* form. The relation between these assignments and those in amides and simple enolates is discussed.

The *E,Z* forms of diacetamide (**1**) and the isoelectronic enolate anion acetylacetonate (**2**) exhibit large chemical



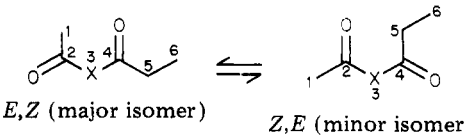
Z,Z



E,Z

1, X = NH
2, X = CH^-

shift differences between diastereotopic carbonyl and/or methyl groups in their ^1H and ^{13}C NMR spectra.[2-4] Assignments of resonances to the *Z,Z* and *E,Z* diastereomers of these and other symmetrical imides and β-diketone enolates can be made on symmetry grounds, since the *E,Z* forms exhibit pairs of resonances for diastereotopic acyl groups while the *Z,Z* diastereomers exhibit only a single resonance for the homotopic acyl groups.[3-5] However, it is not possible, on the basis of the spectra of the symmetrical compounds alone, to assign the pairs of resonances in the *E,Z* diastereomers to the diastereotopic *E* and *Z* acyl groups. This paper describes an approach, using the unsymmetrical homologues of **1** and **2**, viz., *N*-acetylpropionamide (**3**) and propionylacetonate (**4**), to make these assignments and provides information about the effects of neighboring acyl groups on ^1H and ^{13}C NMR chemical shifts which may be useful in making assignments in other compounds.



E,Z (major isomer) *Z,E* (minor isomer)

3, X = NH
4, X = CH^-

It might have been supposed that the magnetic an-

(1) (a) This paper can be considered part of two series: "NMR Studies of Enolate Anions. 7." and "Stereochemistry of Trivalent Nitrogen Compounds. 37." For previous papers in these series see: "NMR Studies of Enolate Anions. 6." (Raban, M.; Haritos, D. P. *J. Am. Chem. Soc.* **1979**, *101*, 5178) and "Stereochemistry of Trivalent Nitrogen Compounds. 36." (Raban, M.; Lauderback, S. K. *J. Org. Chem.*, in press). (b) We thank the National Science Foundation and the National Institute of General Medical Sciences for support of this work. (c) A portion of this paper was abstracted from a thesis submitted by D.H. in partial fulfillment of the requirements of the M.S. degree, Wayne State University.

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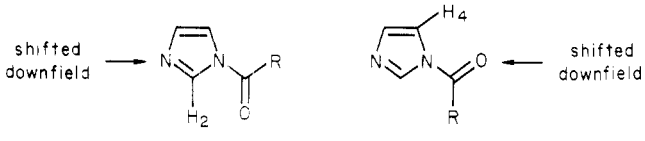
0022-3263/80/1945-2672$01.00/0

Table I. ^1H and ^{13}C Chemical Shifts in 1-4[a]

			^1H		^{13}C					
	solvent[b]	config	CH_3[c]	CH_2	C-1	C-2	C-3	C-4	C-5	C-6
1	methanol	*E,Z*	2.13 (*Z*), 2.42 (*E*)		26.4 (*E*)	175.1 (*E*)		172.1 (*Z*)	24.4* (*Z*)	
	methanol	*Z,Z*	2.13		24.1* (*E*)	171.6 (*E*)		171.6 (*Z*)	24.1* (*Z*)	
	acetone	*E,Z*	2.18 (*Z*), 2.38 (*E*)		25.7 (*E*)	173.2 (*E*)		170.8 (*Z*)	24.4 (*Z*)	
	acetone[d]	*Z,Z*	2.18							
	CH_2Cl_2	*E,Z*	2.17 (*Z*), 2.46 (*E*)							
2[e]	methanol	*E,Z*	1.89 (*Z*), 2.27 (*E*)		26.5 (*E*)	194.4 (*E*)	102.2	192.6 (*Z*)	28.9 (*Z*)	
	methanol	*Z,Z*	1.80		28.0 (*E*)	190.4 (*E*)	99.2	190.4 (*Z*)	28.0 (*Z*)	
3[h]	acetone	*E,Z*[f]	2.38	*g*	25.2	173.0		173.9	*g*	8.5
	acetone	*Z,E*	2.15	2.78	24.2	170.6		176.4	*g*	8.5
	CH_2Cl_2	*E,Z*[f]	2.48	2.46	26.7	174.2		176.5	30.2	8.2
	CH_2Cl_2	*Z,E*	2.17	2.88	25.1	170.8		179.6	31.9	8.2
4[h]	methanol	*E,Z*[f,i]	2.27	1.81	26.7	194.9	101.1	197.2	36.3	12.1
	methanol	*Z,E*[i]	2.02	1.87	29.1	192.0	101.1	198.9	32.6	11.13
	methanol	*Z,Z*[i]	1.81	2.09	27.5	190.9	97.9	194.9	35.6	12.5

[a] Assignments were not certain for resonances indicated with asterisks and may be reversed. Chemical shifts are reported in δ relative to tetramethylsilane. [b] Deuterated solvents were used for all ^1H NMR and some ^{13}C NMR spectra. [c] Acetyl methyl. [d] Separate resonances could not be resolved for the *Z,Z* form in acetone as solvent. However, increased intensity of the upfield resonance indicated that the *Z,Z* isomer also resonates at this frequency. [e] Taken from ref 3. [f] Major isomer. [g] Peak overlap with solvent. [h] The propionyl methyl did not exhibit measurable nonequivalence and appeared at δ 1.12 for 3 and δ 1.07 for 4. [i] The ^1H NMR chemical shifts for 4 are derived from spectra of the compound in the presence of LiI (*Z,Z* form) and 18-crown-6 (*E,Z* and *Z,Z* forms).

isotropy of the imide carbonyl group would be similar to that of the ketone or aldehyde carbonyl group and that the effect of the carbonyl group in the *Z* acyl group of *E,Z*-1 (and by extension *E,Z*-2) would result in a downfield shift for the *E*-acetyl methyl group in ^1H NMR spectra. Indeed, chemical shift assignments in diformamide[2] (5) and *N*-acylimidazoles[6] (6) are in accord with this supposition. In diformamide (HCONHCHO), where assignments can be rigorously made on the basis of vicinal coupling constants, the *E*-formyl hydrogen exhibits a downfield shift of 0.55 ppm relative to the *Z* carbonyl group. *N*-Acylimidazoles exist as mixtures of *E* and *Z* isomers which are analogous to the *E,Z* and *Z,Z* diastereomers of imides. A variety of evidence was used in making assignments which were consistent with the supposition that the amide acyl group effects downfield shifts on ring protons near to and in the nodal plane of the carbonyl group.



Z-6 *E*-6

Although the assignments for 5 and 6 are in accord with a simple model for carbonyl anisotropy, extrapolation to the dialkyl analogues 1 and dipropionamide was not deemed to be reliable because of the ambiguity about the effect of the amide carbonyl group in simple amides.[7,8] This ambiguity can be illustrated by the behavior of the *N,N*-dialkylacetamides. While the simple anisotropic model would predict, for *N,N*-dimethylacetamide, that the *N*-methyl group syn to the carbonyl oxygen atom should appear downfield with respect to the anti methyl group, the relative observed shifts in nonaromatic solvents are reversed from this prediction. The situation in *N,N*-diethylacetamide is even more complex. Here the shifts of the *N*-ethyl methylene groups are reversed from the *N*-methyl shifts in *N,N*-dimethylacetamide. Thus, the syn methylene group appears downfield with respect to the anti methylene group. By contrast, the *N*-ethyl methyl groups resonate in reversed order from those of the methylene groups and in the same order as in dimethylacetamide; i.e., the syn methyl group appears upfield.

One explanation[9] offered for this behavior involved the averaged positions of the protons with respect to the nodal plane of the amide group. It was argued that protons should experience downfield shifts when in the nodal plane but would lie within the shielding region of the amide group when they were out of the plane. On the basis of this kind of reasoning it would seem reasonable to question whether the assignment of diformamide, where the *E*-formyl hydrogen lies in the nodal plane of the *Z* formyl group, could be safely generalized to diacetamide where the acetyl methyl protons project out of the nodal plane. Examination of an unsymmetrical imide provided one way for us to solve this problem and we have also examined the enolate analogues for which a comparable ambiguity exists.

Results and Discussion

At −90 °C the ^1H NMR spectrum of diacetamide in dichloromethane features two acetyl methyl resonances of nearly equal intensity (Table I), indicating that torsion about the C–N partial double bonds is slow on the NMR time scale at this temperature and that the molecule exists nearly completely as the *E,Z* configuration.[2] The fairly large chemical shift difference for the two acetyl methyl groups (0.29 ppm) suggests that the shift difference reflects the anisotropy of the carbonyl function. The same chemical shift difference is observed in methanol, although in this solvent the upfield resonance (at δ 2.13) is considerably more intense, indicating that a substantial amount of the *Z,Z* form exists in this solvent and that its resonance cannot be resolved from that of the upfield *E,Z* acetyl methyl group. The resonances of the two diastereomers, however, can be resolved in the ^{13}C NMR spectra measured at 25 MHz, although in this case as well, the resonances (carbonyl and acetyl methyl) of the *Z,Z* form were very close to those of one of the diastereotopic acetyl groups in the *E,Z* diastereomer. The three carbonyl resonances were of nearly the same intensity (as were the acetyl

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(9) Paulsen, H.; Todt, K. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 899; *A. Anal. Chem.* **1968**, *235*, 29.

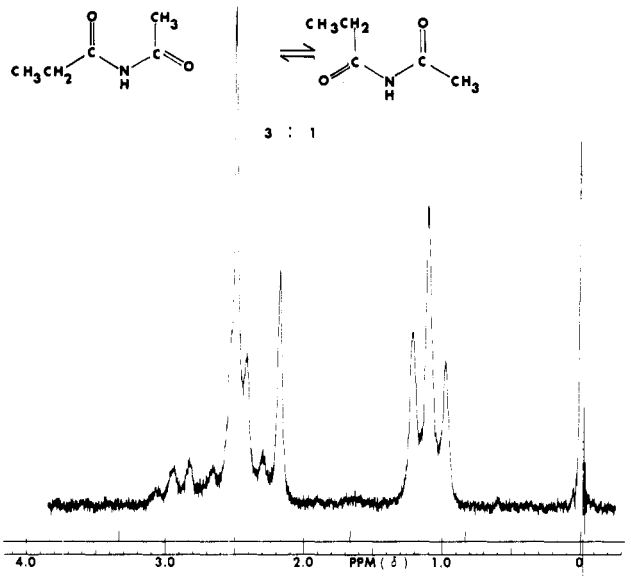


Figure 1. Low-temperature ^1H NMR spectrum of **3** in CD_2Cl_2.

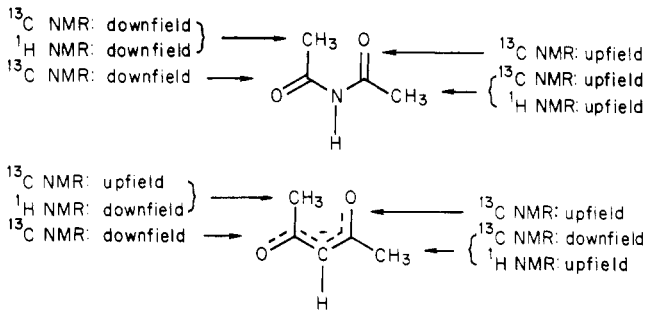
methyl resonances), indicating an $(E,Z)/(Z,Z)$ ratio of about 2:1 and preventing assignment from being made to starred resonances in Table I. The ^1H NMR spectrum in acetone was comparable to that in methanol in that only two unequal acetyl methyl resonances were observed. The upfield resonance was slightly more intense, indicating the presence of about 5% of the Z,Z form as compared with 34% in methanol.

The low-temperature ^1H spectrum of the unsymmetrical analogue **3** indicates the presence of two diastereomers (E,Z and Z,E) which correspond to the two E,Z topomers of **1** in a ratio of about 3:1 (Figure 1). We assign the Z,E configuration to the minor isomer since in this isomer the bulkier alkyl group, ethyl, is in the more congested environment close to the oxygen atom of the other acyl group. In this isomer the hydrogens of the E-propionyl methylene group appear downfield while the Z-acetyl methyl group is upfield with respect to the corresponding resonances of the major E,Z diastereomer of **3**. On this basis we may conclude that the downfield methyl resonance in **1** corresponds to the E acetyl group and the upfield resonance to the Z acetyl group (Chart I). These assignments are in the same direction as those in diformamide and acylimidazoles and do not exhibit the anomalous behavior described above for simple amides. The behavior of the simple N,N-dimethyl amides had been associated with nonplanarity of acetyl methyl, a factor which is also present here. However, it is known that the imide group is planar at nitrogen while amides exhibit nonplanarity at nitrogen.[2] It may be that the geometry at nitrogen is more important than has been previously thought.

The low-temperature ^{13}C spectra of **3** likewise reflect the presence of two diastereomers in the region of the acetyl and propionyl carbonyl carbon atoms and in the region of the acetyl methyl and (in CD_2Cl_2 as solvent) propionyl methylene groups. Both the carbonyl carbon atoms and the methyl or methylene carbon atoms attached to them in the E acyl group (C-1 and C-2 in the major isomer and C-4 and C-5 in the minor isomer) appear at lower field than their counterparts in the other diastereomer. On this basis we may assign the downfield methyl and carbonyl resonances of **1** to the E-acetyl carbon atoms.

These orders of methyl and methylene chemical shifts, like those in the ^1H NMR spectra discussed above, are at variance with the predictions which might have been made on the basis of assignments in simple N,N-dialkyl amides.[10-12] The two N-methyl groups in N,N-dimethylformamide have been assigned on the basis of the spectra of the two (E and Z) diastereomers of N-methylformamide.[10] The resonance of the *pro-Z*-methyl group, which is syn to the carbonyl oxygen, appears upfield with respect to that of the *pro-E*-methyl group. This order of resonances was attributed to a steric shift of the *pro-Z*-methyl group occasioned by its proximity to the carbonyl oxygen. A similar order is observed in N,N-dimethylacetamide, whose shifts were assigned via a specific ^1H decoupling experiment.[11] If the order of shifts is to be attributed to a steric shift in the latter case as well, as has been suggested,[10] it must be argued that the carbonyl oxygen gives rise to a greater steric shift than methyl.

Chart I



In the present case, it seems clear that if steric shifts were the sole determinant of the relative shifts of the methyl groups in **1** and **3**, those in the E-acetyl methyl groups should appear upfield with respect to those of the Z acetyl groups. Consequently, we must assume that factors other than steric effects are responsible for the downfield shifts of the E-acetyl methyl groups in N-acylacetamides **1** and **3**. One possibility is that small changes in torsion angles at the amide bonds can have significant effects on the magnitude of π bonding, which is reflected in carbon chemical shifts.

A similar procedure was used to make assignments in the isoelectronic enolate anions. The resonances of the sodium salt of acetylacetonate in methanol indicate three kinds of acetyl groups in either ^1H NMR or ^{13}C NMR spectra.[3,4] Again, we have assigned equally intense signals to the major E,Z isomers and the remaining signal to the less populated chelated Z,Z diastereomer. The spectra of the unsymmetrical analogue features resonances from three isomers, the chelated Z,Z form and dissociated E,Z and Z,E forms. Assignments in the ^{13}C NMR spectrum could be made in a straightforward manner. The resonances of the Z,Z form were identified by addition of LiI to the sample. This converted all of the sample to the chelated Z,Z form; the remaining resonances were assigned on the basis of their relative intensities and the shifts relative to those of the Z,Z diastereomer which were derived from the spectrum of **2**. Examination of the ^1H NMR spectrum was hampered by overlap of signals from all three isomers. In this case as well, the spectra were simplified, here by addition of 18-crown-6 which completely converted the sample to the E,Z configuration and LiI which shifted the equilibrium completely to the chelated Z,Z form.[3,4] Examination of the data in Table I and summarized in Chart I indicates that, in this case as well, proximity of the E-acyl methyl or methylene group to the oxygen of the other carbonyl group is associated with a downfield shift in the

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^{1}H NMR spectra. The carbonyl shifts in the isoelectronic analogues are also in the same direction; viz., the *E* acyl groups correspond to the downfield carbonyl resonances. However, the acetyl methyl (and propionyl methylene) shifts in the ^{13}C NMR spectra are different in the two systems. In the imide system proximity to the oxygen of the other carbonyl (i.e., the *E* configuration) is associated with a downfield shift while in the enolate system an upfield shift is observed.

The differences between these two isoelectronic systems as well as the differences between the assignments made here and those which have been made for simple *N,N*-dialkyl amides illustrate the difficulty in making a priori predictions and in extrapolating from one system to another, especially when the origin of the relative shifts is not well understood.

Experimental Section

Low-temperature (ca. −90 °C) ^{1}H NMR spectra were measured at 60 MHz on a Varian A60-A spectrometer equipped with a V-6040 variable-temperature controller. Low-temperature (ca. −90 °C) ^{13}C NMR spectra (except for that of **1**) were measured at 15.04 MHz on a JEOL FX-60 spectrometer with broad-band proton-noise decoupling. The NM 5471 variable-temperature controller was modified to use nitrogen gas which passed through coils cooled in liquid nitrogen. The ^{13}C NMR spectrum of **1** was measured at 25 MHz on a JEOL FX-100 spectrometer. Spectra were measured on 0.4 M solutions in 10-mm tubes. Diacetamide, acetylacetone, and hexane-2,4-dione were obtained commercially. *N*-Acetylpropionamide was prepared as described previously:[13] mp 85.5–86.5 °C (lit.[13] mp 86–87 °C). The sodium enolates were prepared by the dropwise addition of the β-diketone (11 mmol) in benzene or pentane to a benzene or pentane slurry of oil dispersed sodium hydride (0.547 g, 10 mmol, 57% oil dispersion). The mixture was stirred until the evolution of hydrogen gas ceased. The precipitate was filtered, washed with benzene, and dried in vacuo.

Registry No. 1, 625-77-4; 3, 19264-34-7; 4, 72844-58-7.

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Amine Catalysis of the Hydrolysis of Trifluoroacetanilide

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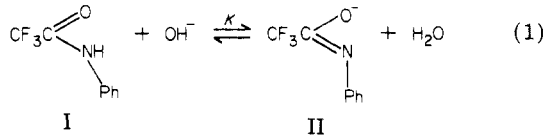
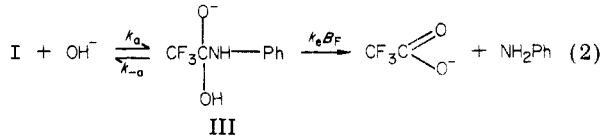
Only hydrolysis products could be isolated from the reaction of trifluoroacetanilide I with aqueous *n*-butylamine buffer at pH 10.5. Kinetic studies of the decomposition of trifluoroacetanilide I in aqueous morpholine, *n*-butylamine, piperidine, and trimethylamine buffers were also conducted. The most reasonable scheme for the reaction mechanism, compatible with all data, is presented in Scheme I and involves the general-base-catalyzed decomposition of the intermediate III which can be formed by hydroxide ion or water addition to I. Utilizing the constants of Table I, eq 6 is capable of predicting observed rate constants with an error of less than 9% (see Tables II and III). Some variation in values for these constants for trimethylamine buffers is observed and attributed to possible activity changes for the solutions. Deuterium isotope rate effects were determined for these constants in morpholine buffers. A value of $k_1^{H_2O}/k_1^{D_2O}$ of 0.39 was obtained and may indicate the presence of a third pathway for the generation of III (eq 9), involving the hydration of the anion II. A value of $k_4^{H_2O}/k_4^{D_2O}$ of 1.65 and a Brønsted β value of 0.23 for k_4 are interpreted to indicate general-base catalysis by the amine buffer. The low values for these quantities are indicative of a transition state involving an early proton transfer. General-base catalysis of proton transfer for the k_4 step is also indicated by the fact that trimethylamine appears to behave mechanistically, similar to the other amines used. The value of 8.8 obtained for $k_3^{H_2O}/k_3^{D_2O}$ clearly shows proton transfer to be occurring in this step as well. The results of this study thus support those suggested previously in that the hydrolysis of I undergoes a change in rate-determining step in mild alkaline aqueous solutions. This occurs because of the combination of the poor leaving ability of the anilinium ion and acyl activation present in the substrate trifluoroacetanilide.

2,2,2-Trifluoroacetanilide (I) is known to hydrolyze in mildly alkaline solutions.[1] The reaction is considerably faster than the alkaline hydrolysis of acyl-unactivated amides and appears to be catalyzed by a number of well-known general bases.[2-5] Acyl activation has not only increased the reactivity of this amide but has similarly affected its acidity; the probable pK_a being in the vicinity of 9.5 compared to "normal" values of approximately 15.[6] The mechanism of the reaction is believed to involve the general-base-catalyzed decomposition of a preformed tetrahedral intermediate (III) between the substrate and the hydroxide ion (eq 1 and 2).[2,3] Mader has suggested



(1)

I II



(2)

III

that II may hydrate to form III, but there is no evidence

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