[fragment nitrosamine]) vs. t) by linear regression analysis. The error in the rate constant is the standard deviation of the slope. Initial concentrations of substrate and base were determined from "t = 0" samples by chromatographic analysis and titration (as above), respectively, since volumetric glassware was used only to take samples and make up standard solutions. A typical procedure follows: (2-hydroxy-2-phenylethyl)methylnitrosamine (**7**; 0.168 g, 0.93 mmol) and 0.177 g (1.58 mmol) KO-t-Bu were weighed into a previously dried (120 °C) 10-mL serum vial, and the vial was capped with a Teflon-lined rubber serum cap and sealed (metal crimp). *tert*-Butyl alcohol (4 mL) was injected by syringe through the seal, and the vial was placed in a constant-temperature bath at 50 °C after solution was effected by shaking. Samples (0.1 mL) were taken immediately for substrate and base concentration determinations. At the desired time (eight times between 0 and 124 h) a 0.1-mL sample was taken through the serum cap with a precalibrated 500-mL syringe. The contents of the syringe were discharged into 2 mL of THF containing 30 mL of 2.5 M acetic acid in THF. The resulting mixture was diluted to 5 mL with THF and stored at 4 °C until analysis by HPLC on a Partisil 10-ODS column with 35% methanol/water. Both the substrate and DMN were determined (see Table I run 18 (correlation coefficient r = 0.9996)).

Depending upon instrument availability, DMN was sometimes determined by GLC analysis. The procedure was similar: For example, a typical reaction mixture consisted of 0.415 g (3.1 mmol) of **6**, 0.247 mL (2 mmol) of p-xylene, 0.473 mL (5 mmol) of t-BuOH, and 0.56 g (5 mmol) of KO-t-Bu in 8 mL of dry THF. Analytical samples were taken and neutralized in the same way as HPLC and DMN was determined by GLC using a Porapak PS ($^1/_8$ in. × 2 ft column) and the TC detector.

Specialized Experiments To Check for Reversibility. In one type of experiment we attempted to reduce the aldehyde or ketone product with sodium borohydride which was incorporated into the reaction medium in molar amounts equal to the starting nitrosamine. In no case did this procedure change k_{obsd} or the yield of procuct nitrosamine (at a fixed time) from that observed in the absence of $NaBH_4$. We have, however, reason to question the efficacy of this experiment because of our studies on **2** in t-BuOH where reversibility has been detected under fragmentation conditions. The trapping of the carbonyl product by $NaBH_4$ may be more effective in THF.

(2-Hydroxypropyl)methylnitrosamine (**4**; 0.182 g, 1.54 mmol), dimethylnitrosamine (0.365 g 4.92 mmol), and KO-t-Bu (0.62 g 5.5 mmol) were dissolved in t-BuOH (3.055 g) and heated in a sealed vial at 70 °C. Fourteen samples were withdrawn over the course of 167 h (90% reaction). The disappearance of **4** and the yield of DMN was the same as in a run containing no DMN [k_{obsd} = 2.9 × 10^{-6} s^{-1} compared to 3.1 × 10^{-6} s^{-1} (run 6)]. Attempts to use acetaldehyde to test the reversibility in the same way were unsuccessful because of its rapid consumption in the strongly basic media.

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Registry No. **2**, 26921-68-6; **3**, 1116-54-7; **4**, 75411-83-5; **5**, 36972-72-2; **6**, 50597-30-3; **7**, 36972-73-3; (1*R*,2*S*)-**8**, 7181-48-8; **9**, 36972-76-6; **10**, 83334-32-1; **11**, 62-75-9; **12**, 4549-40-0; ethylmethylnitrosoamine, 10595-95-6.

Kinetic Demonstration of the "Syn Effect" in β-Hydroxy Nitrosamine Fragmentation

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The base-induced fragmentation rate of β-hydroxy nitrosamines is subject to striking control by the stereochemical orientation of the *N*-nitroso function. (*Z*)-(2-Hydroxy-2,2-diphenylethyl)methylnitrosamine (**1Z**) is cleaved to dimethylnitrosamine and benzophenone (k_{obsd} = 6.8 × 10^{-3} s^{-1}) 287 times more rapidly than an equilibrium mixture of the *Z* and *E* isomers (13:87) at 35 °C in *tert*-butyl alcohol containing potassium *tert*-butoxide. The rate constant for the fragmentation of the equilibrium mixture (k_{obsd} = 2.37 × 10^{-5} s^{-1}) is similar in magnitude to the rate constant (k_{obsd} = 1.67 × 10^{-5} s^{-1}) for isomerization of the *Z* isomer (syn) to its *E* form. Arguments are presented in support of the hypothesis that the *E* isomer must isomerize prior to fragmentation. This remarkable stereoelectronic control of a C–C bond cleavage five bonds removed from the isomerizing N–NO group is attributed to the greater stability of the incipient syn α-nitrosamino carbanion. A Hammett study of substituent effects on the fragmentation rate of ring-substituted derivatives of **17** gives a ρ = −0.86, indicating modest positive charge development in the transition state. A detailed discussion of the mechanism is presented.

It is well-known that nitrosamines constitute a family of potent, environmentally prevalent, animal carcinogens. A knowledge of the chemistry of putative carcinogens and other toxic environmentally prevalent substances not only is essential to the development of a proper risk assessment for each chemical but also is important in understanding their mode of biological action. Such motivation has led us to the investigation of the retroaldol-like fragmentation of β-hydroxy nitrosamines.

In the previous paper[1] and several other preliminary accounts[2-5] we demonstrated that the base-induced fragmentation reaction of a β-hydroxy nitrosamine is a general reaction of these compounds and proceeds according to eq 1. The reaction rate is a function of the groups R_1–R_3, the base concentration, and the solvent. The reactivity order for the nitrosamino alcohols is tertiary ≫ secondary

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(3) Loeppky, R. N.; Gnewuch, C. T.; Hazlitt, L.; McKinley, W. A. In "*N*-Nitrosamines"; Anselme, J. P., Ed.; American Chemical Society: Washington, DC, 1979; p 109.

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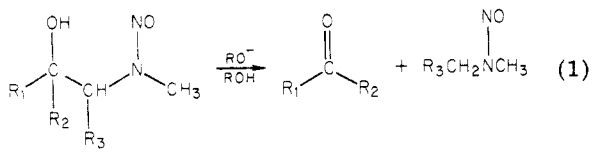


(1)

> primary. A mechanism which accounts for these effects was proposed and involves generation of the substrate alkoxide which undergoes rate-determining C_α–C_β bond cleavage to generate a carbonyl compound and a α-nitrosamino carbanion. The smaller, fragment nitrosamine is generated from the carbanion by proton donation from the solvent. The reaction rate was shown to be influenced by the stability of the incipient carbonyl and nitrosamino carbanion intermediates as well as by steric effects.

Unsymmetrical nitrosamines like those used in our investigation exist in two isomeric forms at room temperature. These isomeric syn and anti or *Z* and *E* forms (e.g., **1E** and **1Z**) result from restricted rotation around the N–N bond (see Scheme I). The β-hydroxy nitrosamines utilized in our investigation of the transformation (eq 1) were mixtures of *Z* and *E* forms containing at least 75% of the *E* isomer (anti to OH). In the course of this work it became apparent that **1Z** undergoes the base-catalyzed fragmentation much more rapidly than **1E**. This paper reports the details of that discovery, evidence supporting the hypothesis that **1E** must isomerize to **1Z** before the molecule undergoes fragmentation, and a Hammett study of the fragmentation of para-substituted derivatives of **1Z**.

The striking stereoelectronic control exhibited by the N–NO function not only is of significance in the area of nitrosamine carcinogenesis but also is of importance to an understanding of the factors which affect stereospecific metalation of nitrosamines and carbonyl derivatives.

Results

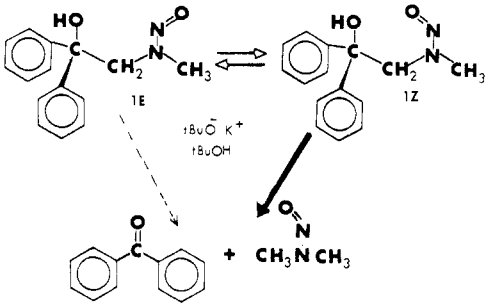
One of us (L.G.H.) desired a safe and facile laboratory method for preparing and following the kinetics of fragmentation of 1 and some of its derivatives. Walser and Silverman[6] have shown that a nitrosamine and a ketone could be condensed in THF (tetrahydrofuran) containing KO-*t*-Bu (potassium *tert*-butoxide) at −20 °C, and in the midst of our work Seebach's group showed that this was true for benzophenone and dimethylnitrosamine (DMN) as well as for other compounds.[7] Following the work of Walser and Silverman,[6] we charged a dry serum sealed vial with a standard solution of DMN and KO-*t*-Bu in dry THF. A solution of benzophenone in dry THF was added to this mixture and the vial allowed to stand at −10° for several hours. Samples were taken and analyzed by HPLC, after neutralization, in order to verify the formation of (2-hydroxy-2,2-diphenylethyl)methylnitrosamine (1). (We shall refer to this as the WS style synthesis.) After this fact was established, the vial was immersed in a thermostated constant-temperature bath at 35 °C, and the fragmentation of 1 was followed by HPLC after neutralization of the aliquots. The results obtained from this "in situ synthesis/fragmentation" experiment are shown in Figure 1 in the form of a ln [1] vs. time plot. This highly curved plot appeared to consist of two linear components and led to the hypothesis that the *Z* and *E* isomers were fragmenting at different rates. To test this hypothesis, we had to separate or synthesize **1Z** and **1E**.

The condensation of benzophenone with (lithiomethyl)methylnitrosamine according to the elegant procedure of Seebach and Enders[8] (the SE synthesis) leads to the synthesis of **1E** after crystallization. The ^1H and ^{13}C NMR spectra of a $CDCl_3$ solution of this substance taken immediately and then again several hours after dissolution demonstrate it to be constituted of a 13:87 equilibrium mixture of **1Z** and **1E** diastereoisomers respectively (35 °C) but to exist exclusively as the *E* form in the crystalline solid. The knowledge that the ^1H NMR signal arising from a CH_3 or CH_2 syn to the *N*-nitroso oxygen is 0.3–0.5 ppm upfield of the corresponding anti proton resonances[9] and a similar relationship in the ^{13}C NMR spectra permits the assignment of the structures to the components of the diastereomeric mixture (chemical shifts in parts per million from Me_4Si) ^1H (^{13}C) NMR for **1Z**: CH_3, 3.43 (41.3); CH_2, 4.62 (55.5); CO (77.9). For **1(E)**: CH_3, 3.00 (34.0); CH_2, 5.02 (63.1); CO (77.9).

HPLC analysis of the equilibrium mixture of **1E** and **1Z** by using a reversed-phase ODS column and 38% methanol–water as an eluant demonstrated that "base-line" separation of these isomers could be achieved under conditions which also permitted the separation and determination of DMN and benzophenone. Since the relative quantities of these substances are known from the NMR, we could assign a structure to the respective HPLC peaks. The *Z* isomer has the greater retention volume. This led to the finding that the WS synthesis of 1 led to the exclusive formation of **1Z**, provided, of course, that samples of the cold mixture were neutralized and analyzed immediately. We presume that the SE synthesis gives, initially, exclusively **1Z** as well but that it isomerizes during normal workup and crystalizes as **1E**.

This information permitted the development of a method for the isolation of **1Z** and its derivatives in nearly pure form. The synthesis of **1Z** is conducted by the SE method except that the hydrolysis is performed by the

Scheme I



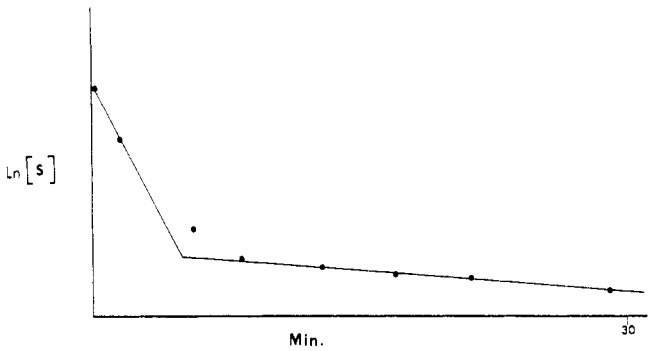


Figure 1. Plot of ln [substrate] vs. time (min) for the "in situ synthesis/fragmentation" of **1Z** following its preparation which shows the curved nature of the ln *S* vs. *t* relationship here (at 35 °C).

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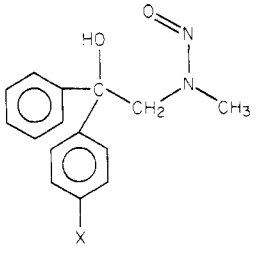
Table I. Rate Constants for the Fragmentation of (Z)-(2-Aryl-2-hydroxy-2-phenylethyl)methylnitrosamine at 35 °C

compd	substituent	$10^{-3}k_{obsd}$, s^{-1}
1Z	H	6.8 ± 0.5
6Z	CF_3	1.65 ± 0.02
7Z	Cl	4.3 ± 0.5
8Z	OCH_3	9.0 ± 0.8
9Z	$N(CH_3)_2$	28 ± 1

addition of 5% aqueous K_2CO_3 (in lieu of acetic acid), and extractions and isolations of the resulting solid are accomplished at temperatures below 5 °C. ^1H NMR analysis of the freshly dissolved product shows it to contain less than 5% of the *E* isomer at the time the spectrum is recorded. Rapid HPLC analysis of **1Z** prepared in this way shows it to contain less the 1% of its *E* isomer. The thermal instability of **1Z** toward isomerization precluded its further purification. The 4-substituted-phenyl derivatives of **1Z** (**6–9**) are prepared from DMN and the appropriate 4-substituted benzophenones by the same method. The four phenyl substituents are CF_3, Cl, OCH_3, and $N(CH_3)_2$.



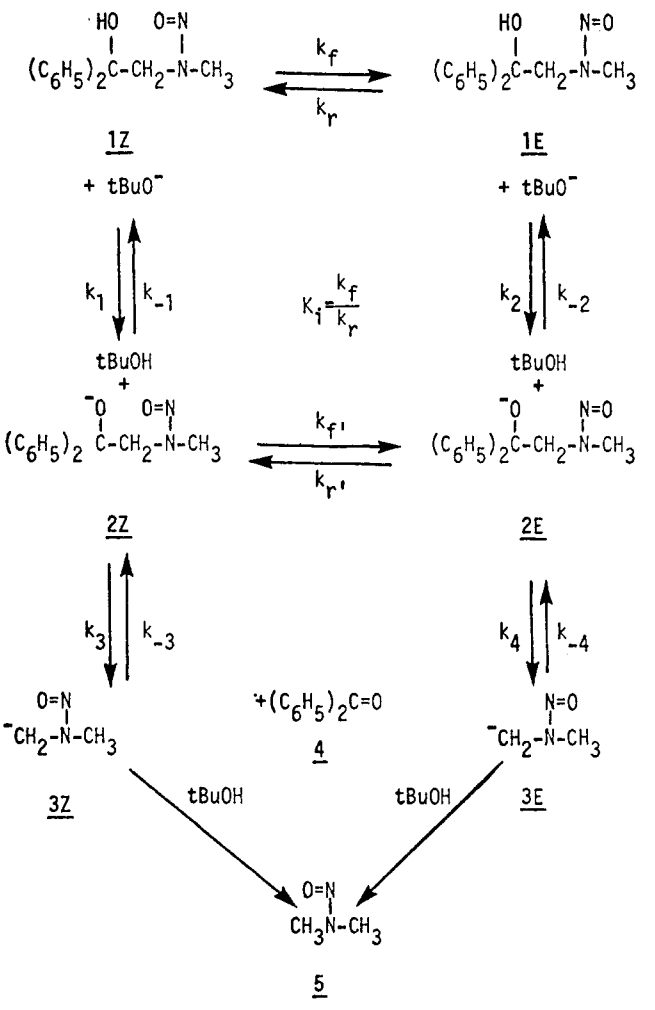
6, X = CF_3
7, X = Cl
8, X = OCH_3
9, X = $N(CH_3)_2$

Kinetic measurements for the fragmentation of **1Z** were performed by making a stock solution of **1Z** in cold THF. An aliquot of this cold solution was added to a standardized solution of KO-*t*-Bu in *t*-BuOH which had been prewarmed to 35 °C. One sample was prepared for each point and at the appropriate time was quenched with acidic methanol–water. After volumetric dilution the samples were analyzed by HPLC and the nitrosamines determined by the use of standard curves. The HPLC utilized a UV detector (254 nm), and we had to assume that the *Z* and *E* isomers had identical extinction coefficients so that standard solutions of the *E*–*Z* equilibrium mixture could be employed for calibration. The rapidity of the reaction permitted only a few points to be taken, but the reaction exhibited good first-order kinetics through complete consumption of the substrate. The rate constant (k_o) obtained for **1Z** is 6.8 ± 0.5 × 10^{-3} s^{-1} (0.9 M KO-*t*-Bu) which yields a $t_{1/2}$ of 102 s. Rate constants (k_x) for the substituted-phenyl derivatives of **1Z** (**6Z–9Z**) are given in Table I and were determined under identical base concentrations (0.9M KO-*t*-Bu). A plot of log (k_x/k_o) vs. the Hammett σ value for the observed rate constants was made and displays good linearity, yielding $\rho = -0.86 \pm 0.08$.

As we have noted previously[1] an equilibrium mixture of **1E** and **1Z** undergoes smooth first-order decomposition to DMN and benzophenone in THF/*t*-BuOH/KO-*t*-Bu or *t*-BuOH/KO-*t*-Bu. The rate constant $k_{E(obsd)}$ obtained from the slope of the first-order plot of ln [substrate] vs. time is (2.37 ± 0.09) × 10^{-5} s^{-1}, and $t_{1/2}$ = 487 min (1.1 M HO-*t*-Bu in *t*-BuOH at 35 °C).

The conversion of **1Z** into its thermodynamically more stable isomer **1E** has been followed by ^1H NMR in $CDCl_3$ and by HPLC at 35 °C in *tert*-butyl alcohol (*t*-BuOH). The HPLC measurements yield an equilibrium constant, K_i = 6.4 (see Scheme II), for the interconversion of **1Z** and **1E** and rate constants k_f = (1.07 ± 0.05) × 10^{-4} s^{-1} and k_r = (1.67 ± 0.06) × 10^{-5} s^{-1} $\Delta G_f^{\ddagger}$ = 23.6 kcal/mol). An estimate of the half-life of **1Z** can be made by assuming that the interconversion of **1Z** ⇌ **1E** has a negligible entropy ($\Delta S \approx 0$). The value so obtained at an isolation temperature of 5 °C is 129 h and indicates negligible conversion of **1Z** to **1E** during the isolation time, as was confirmed by our analysis.

Scheme II



Discussion

The very rapid fragmentation of **1Z** in comparison with the equilibrium mixture of the two isomers, which is predominantly **1E**, and the near equivalency of $k_{E(obsd)}$ and k_r permit the construction of a hypothetical mechanistic format such as that given in Scheme II. We propose that the fragmentation of **1E** occurs by rate-determining isomerization of **1E** to **1Z** which then undergoes rapid base-catalyzed C_α–C_β bond cleavage to produce benzophenone **4** and the nitrosamino carbanion **3Z** (the term carbanion is employed loosely and is not meant to exclude a species closely associated with a metal cation). It is the stability of **3Z**, in comparison to its isomer **3E**, which "forces" the *E* isomer to take this cleavage route. We have presented evidence that the fragmentation reaction is endothermic.[1] The transition-state structure will therefore resemble the products and be stabilized by the same factors. There is a great deal of accumulated evidence, including MO calculations, that supports the hypothesis that **3Z** is much

more stable than **3E**.[11-20] Accordingly, the activation energy for **1E** fragmentation must be much greater than that for **1Z**. Experimentally that difference is *at least 3.68 kcal/mol* at 35 °C. The substantiation of this hypothesis follows.

Subsequent to Keefer and Fordor's[10] pervasive discovery of the acidity of the C–H bond adjacent to the nitrosamine function, Fraser,[11-13] Lyle,[14] Seebach,[15] and Barton[16] have convincingly demonstrated that, at the time of its capture by an electrophile (D_2O, R–X, or R_2CO), the α-nitrosamino carbanion prefers an orientation syn and perpendicular to the NNO plane. A good deal of research[11-14] is well summarized by the observation of Fraser and Ng,[12] who examined the H–D exchange rates of the stereochemically distinct four α-protons in a rigid *N*-nitrosodibenzazepine and found that the syn protons underwent KO-*t*-Bu-catalyzed exchange 1000 times more rapidly than the anti counterparts. Axial exchange was favored over equatorial by a factor of 100. From the synthetic perspective the Seebach group[15] and Barton et al.[16] present evidence which supports the conclusion that nitrosamine metalation preferentially occurs syn to the NO function, and these observations have been used to manipulate the regiochemistry of nitrosamino carbanion alkylations.[16] Seebach and colleagues observed a discrepancy between the deuteration and benzophenone condensation stereochemistry of a *N*-nitrosopiperidine and advanced the hypothesis that "hydroxyalkylation" with this ketone was occuring preferentially through an equatorial (rather than the prefered axial) syn α-lithio-*N*-nitrosopiperidine derivative. Evidence was also presented for the partial incursion of a reversible reaction possibly involving a radical anion radical pair generated from the product alkoxide.[15] Their experiments, however, can also be interpreted in a manner consistent with preferred syn axial attack[11-14] and the concept of rapid aldol-like reversal of the conformationally less stable diastereomer (the unobserved product).[17]

The preference for the syn orientation of the carbanion has been shown for a number of systems in addition to nitrosamines. These include the α-lithio derivatives of dialkyl amides, oximes and oxime ethers, hydrazones, ketimines, and aldimines. Recent papers and references contained therein allow a review of the area.[18-21] In one of these papers Houk et al.[18] presented the results of SCF–MO calculations which predict the syn α-nitrosamino carbanion to be more stable than its anti counterpart although the energy difference is not given. This paper confirms the experimental observation that cyclic anti ketimine anions (ring sizes 5–8) are more stable than their syn counterparts in contrast to acyclic ketimine anions. This reversal is caused by a preferred CCN bond angle of 133° which cannot be achieved in the cyclic systems. On the other hand, another set of MO calculations for *N*-(α-lithioalkyl)-*N*-alkyl amides has failed to confirm the experimental observation that the syn anion is prefered.[19] It has recently been demonstrated that interconversion of the syn and anti anions of *N*-alkyl aldimines can be monitored by NMR in the temperature range 30–77 °C,[20] but we are aware of no evidence for this in the nitrosamine system even though it is probable at higher temperatures. There is, therefore, both experimental and theoretical evidence supporting the greater stability of the syn nitrosamino carbanion in comparison to the anti and our task is to examine Scheme II in relation to the experimental kinetic data.

The observed rate law for the disappearance of **1Z** is given in eq 2, where Z_A = [**1Z**] + [**2Z**], the analytical concentration of **1Z** at any time.

$$-dZ_A/dt = k_{Z(obsd)}[Z_A] \quad (2)$$

The fact that $k_{Z(obsd)} \gg k_f$ permits us to exclude the *Z*–*E* isomerization in the derivation of the rate law for the disappearance of **1Z**. Similarly, the observation that no detectable quantity of **1Z** remains at $t = \infty$ allows neglect of the step involving k_{-3} at 35 °C. Assuming the deprotonation–protonation equilibrium (k_1 and k_{-1}) to be fast and reversible, it can be shown that $k_{Z(obsd)}$ is expressed by eq 3, where $k_Z = k_1/k_{-1}$. Although the relationship

$$k_{Z(obsd)} = \frac{k_3 k_Z\,[\text{KO-}t\text{-Bu}]}{K_Z[\text{KO-}t\text{-Bu}] + [t\text{-BuOH}]} \quad (3)$$

between $k_{Z(obsd)}$ and the base concentration has not been determined here, this type relationship has been found to hold for two other β-hydroxy nitrosamines.[1] We have estimated the acidities of nitrosamino alcohols (see ref 1 for details) and find that **1** should be twice as strong an acid as (2-hydroxy-2-phenylethyl)methylnitrosamine which we experimentally determined to have an equilibrium constant analogous to $K_Z \approx 132$, and $k_3 \approx 7.3 \times 10^{-3}$ s^{-1}.

Several important considerations may be taken into account in deriving an expression for the rate of disappearance of the *E* isomer. We note that $k_{E(obsd)}$ is similar in magnitude to k_r and that these rate constants are less than 1% the magnitude of $k_{Z(obsd)}$. Therefore, we may assume that **1Z** and **2Z** meet the criteria of steady-state intermediates. We have also assumed that proton transfers between the alkoxides are fast compared to the isomerization steps (k_f, k_r, k_f', k_r'), and that k_{-3} and k_{-4} are negligible. The analytical concentration of [**1E**] is E_A = [**1E**] + [**2E**], and the experimental rate law is given by eq 4.

$$-d[E_A]/dt = k_{obsd}[E_A] \quad (4)$$

It can be shown that the rate law derived from Scheme I with the assumptions gives the equality for k_{obsd} shown in eq 5, where W_E and K_E are defined as shown.

$$k_{obsd} = \frac{k_r + k_4 + W_E k_r}{1 + W_E} \quad (5)$$

$$W_E = [t\text{-BuOH}]/K_E[t\text{-BuO}^-]$$

$$K_E = [\mathbf{2E}][t\text{-BuOH}]/[\mathbf{1E}][t\text{-BuO}^-]$$

If we assume that K_E and K_Z are of similar magnitude (~132, vide supra) and that $k_r' \approx k_r = 1.67 \times 10^{-5}$, then we estimate $k_4 \approx 7 \times 10^{-6}$. This means that k_3/k_4 (the respective rates of fragmentation of the *Z* and *E* isomers) is approximately 10^3! This value agrees well with Fraser and Ng's[12] finding that the syn/anti H–D exchange rate ratio is 10^3. Since the values of k_r' and k_f' are not known, the actual percentage of the transformation which proceeds through cleavage of **1E** remains a matter of speculation. It is reasonable, however, that the magnitudes of k_r' and

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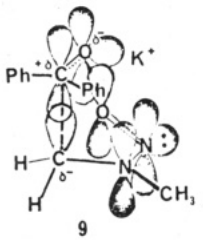
k_f' are greater than those of k_r and k_f. In **2Z** the negatively charged oxygen and the N=O oxygen can experience conformationally dependent electrostatic repulsion through unshared pairs. But this is also a factor in the *E* isomer (**2E**) because the N=O nitrogen has an unshared pair which can repulsively interact with the negative alkoxide oxygen. Steric crowding at the N-bound carbons of nitrosamines is known to increase the isomerization rate by destabilizing either isomer.[22] Thus k_4 may be smaller than estimated, and it is likely that the cleavage of the *E* isomer occurs predominantly by isomerization to the *Z* form which quickly fragments.

The nature of charge development in the transition state for *Z* isomer fragmentation is discernible from the results of the Hammett study which gave $\rho = -0.86$. This indicates that transition state is modestly electron demanding or, in other words, the carbon bearing the phenyl substituents is developing a partial positive charge. Our previous results[1] which showed the rate to increase with the stability of incipient carbonyl compound indicated that ρ might be more negative. Equation 3 shows that k_{obsd} is a function of K_Z. The ρ magnitude may be diminished by the opposite effect of substituents on k_3 and K_Z, and the degree of transition-state C–C bond breaking may be less for the substituted diphenyl β-hydroxy nitrosamines than for the other more endothermic fragmentation reactions which we have examined.

From the preceding information we may construct the depiction of the transition state **9**. As the C–C bond is



9

broken the electron pair on C_α is generated periplanar with the syn NNO π orbital system with which it can interact, thereby providing stabilization for the incipient carbanion. It is not clear from this picture why a syn orientation is preferred.

At least three arguments have been advanced to explain this *syn effect* (see ref 18 or 19 for a review): (a) stabilization of the carbanion by delocalization through a four-atom 6-π-electron system; (b) stabilization of the carbanion by chelation of the metal atom via the syn heteroatom; (c) minimization of dipole–dipole (electrostatic) interactions. The recent MO calculations would appear to favor the importance of the latter explanation.[19] On the other hand, the chelation argument has been advanced to explain the difference between theory and experiment in the amide case.[20] Amides and nitrosamines (amides of nitrous acid) are different in one important respect, that being the presence of the lone electron pair on the N=O nitrogen. Dipole–dipole arguments are likely to be more important, therefore. In order for chelation to be a driving force in the preferred syn isomer fragmentation there must be chelation of the metal ion between the nitroso oxygen and the incipient carbanion in the transition state. Models or reference to the transition-state depiction **9** show that this could impose steric constraints as the metal ion moves from association with the alkoxide oxygen to a position between the nitroso oxygen and the α-carbon (a process involving rotation of the C_α–N bond in order to align the unshared-pair-bearing C_α orbital for overlap with the empty metal orbital). Carbanion additions to the carbonyl are generally considered to involve prior metal ion association with the carbonyl oxygen. Since this retroaldol-like fragmentation is the reverse of such a process, the argument can be made that the metal will remain associated with the procarbonyl oxygen in the transition state. Fraser and Ng found that the addition of a crown ether to complex the metal ion had negligible effect on nitrosamine deuterium-exchange rates,[12] but a chelate could bind the metal ion more strongly than the ether. While these considerations tend to cast doubt on the role that chelation plays in driving the much more rapid fragmentation of the syn nitrosamino alcohol and our data do not permit distinction between it and other modes of syn stabilization, our experimental method has the potential of doing so. The use of kinetic measurements of retroaldol-type reactions as demonstrated here provides an excellent means for determining the relative factors involved in carbanion stabilization and permits a more accurate assessment of steric and stereoelectronic factors since fragmentation rate studies are devoid of the interpretation problems associated with exchange or selective product formation studies.

Since the position of the *N*-nitroso oxygen in a nitrosamine is determined by the steric bulk adjacent to the amino nitrogen, we can predict that β-hydroxy nitrosamines with large groups such as isopropyl, cyclohexyl, or phenyl attached to nitrogen will undergo rapid, base-induced fragmentation to simpler nitrosamines. The results of a test of this hypothesis will be presented in a forthcoming paper.[23] Kupper and Michejda[24] have recently found that nucleophilic reagents, particularly carbanions, add to nitrosamines (vinylnitrosamines), and our results would predict that substrates with bulky nitrogen-attached groups opposite the olefinic group will undergo extremely rapid nucleophilic addition. Our data provide tangible proof that the stereochemistry of the *N*-nitroso function markedly effects the rates of nitrosamine reactions, and it is therefore likely that the rate and course of nitrosamine metabolism, detoxification, carcinogenesis, and environmental formation and transformation is effected as well.

Conclusion

It has been demonstrated that a β-hydroxy nitrosamine with the NO function syn to the OH-bearing alkyl group undergoes much more rapid fragmentation than its anti isomer. It appears that the anti form must isomerize to its syn counterpart prior to fragmentation, and in the case studied here the isomerization was rate controlling for **1E**. The more rapid fragmentation of the syn isomer is related to the greater stability of the incipient syn carbanion. The transition state for the fragmentation involves the development of a partial positive charge at C_β and a partial negative charge at C_α which is generated in such a manner as to permit delocalization by the N–N–O π system. These studies demonstrate that the kinetics of retroaldol-like fragmentations can be utilized to examine the factors which control carbanion stability such as the syn effect in other systems.

Experimental Section

Caution. Nitrosamines are potent animal carcinogens. A workable safety protocol can be obtained by writing the principle author.

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Table II. Properties[a] of (2-Aryl-2-hydroxy-2-phenylethyl)methylnitrosamines

aryl group	no.	mp, °C	formula
4-(trifluoromethyl)phenyl	6	135-136	$C_{16}H_{15}F_3N_2O_2$
4-chlorophenyl	7	107-108	$C_{15}H_{15}ClN_2O_2$
4-methoxyphenyl	8	109-110	$C_{16}H_{18}N_2O_3$
4-(dimethylamino)phenyl	9	156-157	$C_{17}H_{21}N_3O_2$

[a] Satisfactory C, H, and N analytical data were obtained for all compounds in the table.

General Methods. The analytical chromatographic equipment employed here consisted of a MicroTec 2000 R GC with an FID detector, a Varian Aerograph GC with a TC detector, and a "homemade" HPLC consisting of a Haskell air-driven pump (3000 psi maximum), a Rheodyne fixed-loop injector, the column, and an ISCO UV monitor (254 nm). The output from the two GC's and the HPLC instruments was fed into a Columbia Scientific SRS 208 integrator which generated a printed output of peak area vs. retention time. IR spectra were taken on a Perkin-Elmer 237B spectrometer. NMR spectra were either obtained on a Varian EM360 instrument or a Bruker HX90 FT NMR. Mass spectra were obtained from a Du Pont 292 mass spectrometer connected to a Varian gas chromatograph. Melting and Boiling points are uncorrected. Chemicals, except those given below, were obtained from commercial sources and purified as necessary.

Synthesis of (*Z*)-(2-Aryl-2-hydroxy-2-phenylethyl)-methylnitrosamines. The substances used in this work were prepared form the appropriate 4-substituted benzophenone and dimethylnitrosamine by a slight modification of the method of Seebach and Enders.[8] Except for 1, none of these compounds has been reported. Samples for combustion analysis were obtained by recrystalization of the *Z* isomers from hot ethanol, thereby permitting thermal *Z*–*E* equilibration to predominantly give the *E* isomers. Physical constants are given in Table II. The synthetic procedure was the same as that of Seebach and Enders except that 7.5 mmol of ketone was employed per 10 mmol of DMN. After 1.5 h at −78 °C the following workup procedure was employed with precooled (0 °C) equipment, solvents, and solutions. The contents of the reaction flask were poured into a separatory funnel containing a saturated aqueous solution of sodium bicarbonate and ether. The layers were separated rapidly after shaking, and the cold ether solution was dried over anhydrous sodium sulfate in a refrigerator freezer. The ether from the dry solution was removed in vacuo, keeping the product cold. The resulting solid was washed with a small portion of cold hexane and used in the kinetic studies without further purification. The ^{1}H NMR spectrum of **1Z** so obtained is given in Figure 2b of the supplementary material.

Kinetic Experiments. The fragmentation of **1E** has already been described, and the rate constant used here was obtained in *t*-BuOH containing 1.1 M KO-*t*-Bu at 35 °C.[1] The methods for following the fragmentation kinetics and determining rate constants are the same as those described previously except for the special procedures utilized for the determination of the rate constants for the *Z* isomers. The procedure is as follows. A sealed serum vial for each kinetic point is charged with 1 mL of a 0.9 M solution of KO-*t*-Bu in *t*-BuOH. A cold stock solution of the substrate is prepared in THF, and the substrate concentration is determined by HPLC analysis by using standard curves. A 250-mL aliquot of this substrate solution is added to the standard base solution which is preincubated at 35 °C. The reaction is allowed to proceed, and samples for analysis are obtained by stopping the reaction by the addition of acidic methanol. The entire mixture is brought to a volume of 2 mL with methanol, and the concentrations are determined by HPLC analysis within 30 min. Because of the reaction velocity and the stringent requirements of the method, only four or five points were taken. The rate constants obtained from plots of either ln [substrate] as ln $[(S_o - DMN)/S_o](\ln (1 - \nu))$ vs. time and are reported in Table I.

Isomerization Kinetics of (*Z*)- and (*E*)-(2-Hydroxy-1,1-diphenylethyl)methylnitrosamine (1E and 1Z). The kinetics of isomerization of **1Z** to **1E** was followed in two independent ways. A sample of cold **1Z** was dissolved in $CDCl_3$ and the rate of appearance of **1E** followed by ^{1}H NMR by using peak integration for quantitation. The NMR probe was maintained at 35 °C. The other method involved the dissolution of **1Z** in *t*-BuOH. The solution in a sealed serum vial was placed in a thermostated bath at 35 °C, and samples were withdrawn periodically and injected into the HPLC instrument for quantitation. Base-line separation of the isomers was achieved on a Whatman C_{18} reversed-phase Partisil column with 38% methanol water as an eluent. The flow rate was 1.5 mL/min. The retention volume of **1E** was 22.5 mL, and that of **1Z** was 27 mL. Since the transformation is initially far from equilibrium, a plot of ln [**1Z**] vs. time gives a slope of k_f ($1.07 \pm 0.05 \times 10^{-4}$ s^{-1}). Determination of the equilibrium constant by determining the concentration of **1Z** and **1E** at equilibrium by HPLC gave a value of $K_i = 6.4$. This led to the determination of $k_r = k_f/K_i = 1.67 \pm 0.06 \times 10^{-5}$ s^{-1}.

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Registry No. **1**, 36972-76-6; **6**, 83268-47-7; **7**, 83268-48-8; **8**, 83268-49-9; **9**, 83268-50-2.

Supplementary Material Available: ^{1}H NMR spectra of **1E** and **1Z**, Hammett plot for **1Z** and **6–9Z**, and a reaction coordinate diagram for the condensation–fragmentation given in ref 15 with another possible interpretation (7 pages). Ordering information is given on any current masthead page.