With the single exception noted above, all the outliers correspond to structures in which two *tert*-butyl groups are attached to a tricoordinate carbon atom (△ and + in Figure 2). There is also a scatter of such points in the C_2 region but none in the $C_{2v}(2/2)$ and $C_s(2/1)$ regions. These results imply that the barrier to correlated con- or disrotation in compounds of this type may be significantly higher than 1 kcal mol^{-1}, a conclusion that is in harmony with EFF calculations[10] on *cis*-di-*tert*-butylethylene. According to these calculations, enantiomerization of the C_2 ground state structures by correlated conrotation through a $C_{2v}(2/2)$ transition state requires 3.9 kcal mol^{-1} and correlated disrotation through a $C_s(2/1)$ transition state 2.4 kcal mol^{-1}.

Acknowledgment. We thank the National Science Foundation (CHE-8009670) for support of this work.

Registry No. 1, 1070-87-7.

Base-Induced Fragmentation of β-Hydroxy Nitrosamines

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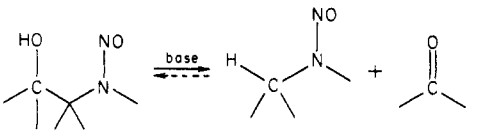
β-Hydroxy nitrosamines have been found to undergo a base-induced fragmentation reaction. The reaction cleaves the C_α–C_β bond of the substrate to produce an aldehyde or ketone and a smaller alkylnitrosamine. Rate constants for the fragmentation induced by potassium *tert*-butoxide in THF or *tert*-butyl alcohol have been measured for nine substrates at temperatures between 35 and 70 °C. The rate constants are a function of base concentration and range between 0.15×10^{-6} and 308×10^{-6} s^{-1}. Rate constants have been determined for (2-hydroxyethyl)methylnitrosamine, *N*-nitrosodiethanolamine, (2-hydroxy-2-methylpropyl)methylnitrosamine, (2-hydroxy-2-phenylethyl)methylnitrosamine, *N*-nitrosoephedrine, (2-hydroxy-2,2-diphenylethyl)methylnitrosamine, and (2-hydroxy-2-phenylpropyl)methylnitrosamine. The nitrosamino alcohol fragmentation rates are in the order tertiary > secondary > primary, and the rate appears to be a function of product stability and steric strain in the substrate. A mechanism which accounts for these observations is proposed.

Several years ago we reported that β-hydroxy nitrosamines appear to undergo a base-induced cleavage reaction to a smaller nitrosamine and a carbonyl compound as is illustrated in eq 1. In this paper we present the general



(1)

characteristics of this transformation.[1,2] Particular attention is given to the structural features which control the relative rates of this transformation, and rate constants are presented for the cleavage of a number of different substrates.

It is well-known that nitrosamines form a large family of potent animal carcinogens.[3,4] The low species selectivity and the high potency of these carcinogens in animal experiments suggest that they may be important in human cancer as well. Because of the ubiquity of their precursors (amines and nitrite) nitrosamines have been found in a wide variety of environmental samples.[4] Of particular relevance to this paper is the occurrence of *N*-nitrosodiethanolamine (NDELA) in metal working fluids,[5,6] cosmetics,[7] shampoos,[7] and tobacco.[8] Recent animal experiments have shown NDELA to be a potent animal carcinogen,[9] and a number of other β-hydroxy nitrosamines are known to be carcinogenic as well.[10]

β-Hydroxy nitrosamines are often formed by the biochemical oxidation of alkylnitrosamines.[10] Because of their

Chart I

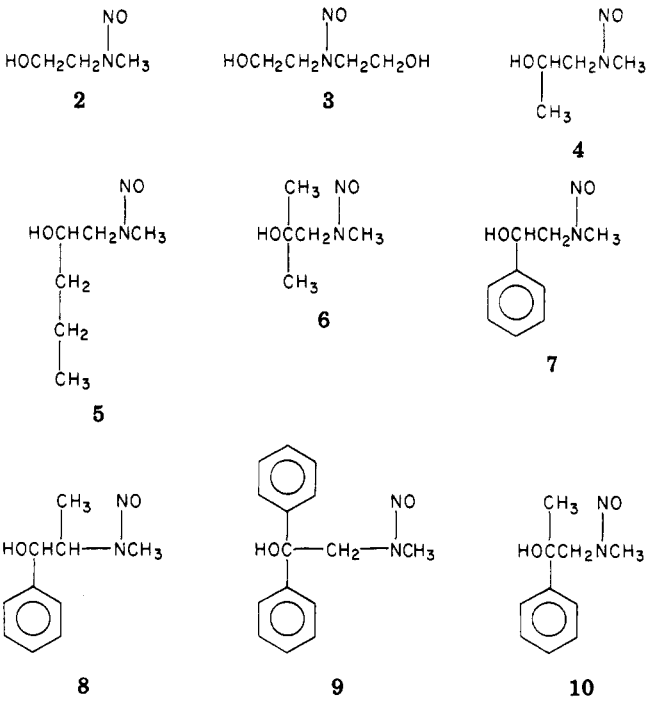


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Table I. Rate Constants for the Base-Induced Fragmentation of β-Hydroxy Nitrosamines

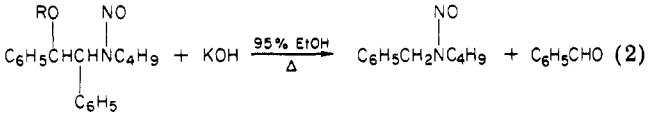
run	substrate	$10^{-6}k_{obsd}$, s^{-1}	error[a]	[base], M	[base]/[substrate]	temp, °C	solvent[b]
1	2	5.3[c]	0.9	0.371	1.32	67	A
2	2	3.19	0.08	0.58	1.33	70	B
3	2	2.82[d]	0.1	0.59	1.28	70	B
4	3	12.1[c]	4	1.02	6	67	A
5	4	2.2	0.1	0.59	1.35	70	B
6	4	3.1	0.1	1	1.54	70	A
7	4	2.4	0.1	1.1×10^{-2}	6	70	A
8	5	167	6.0	0.59	1.32	70	B
9	5	0.25	0.02	0.405	1.47	50	A
10	5	8.1	0.4	1×10^{-2}	6	70	A
11	6	308	20	0.59	1.32	70	B
12	6	97	6	0.72	1.58	50	B
13	6	2.2	0.05	0.34	0.73	50	C
14	6	185	10	0.34	0.73	50	D
15	6	2.8	0.2	0.35	1.5	50	A
16	6	16.2	0.8	0.10	0.75	50	E
17	7	2.22	0.03	0.34	1.44	50	A
18	7	2.08	0.03	0.37	1.70	50	A
19	7	0.47	0.01	0.47	2.94	35	B
20	7	0.42	0.01	0.39	2.17	35	
21	8	1.28	0.06	0.49	2.0	50	A
22	9	42	1	0.39	1.67	50	A
23	9	23.7	0.9	1.1	1.0	35	A

[a] One standard deviation in the same unit as k_{obsd}. [b] Solvent: A = *t*-BuOH, B = THF with 1 equiv of *t*-BuOH/equiv of *t*-BuO^-K^+, C = THF with 0.03 M *t*-BuOH, D = THF with 0.003 M *t*-BuOH, E = HMPA. [c] Estimate from initial rate. [d] Rate of substrate loss (more than one product).

more ready water solubility they are often found as urinary metabolites. But most of these compounds are, like their precursors, carcinogenic. Consideration of published work on the biochemical transformations and metabolism of nitrosamines led us to propose the existence of a biochemical fragmentation of β-hydroxy nitrosamines.[1,10-12] Some analytical procedures for the determination of nitrosamines call for the treatment of the environmental or biological sample with strong alcoholic base.[13,14] The artifactual production and consumption of nitrosamines in these samples could occur through the incursion of the reaction shown in eq 1 and, taken together with the possible biochemical significance of this transformation, provides ample reason for seeking an understanding of this cleavage reaction.

Results

The base-induced fragmentation of β-hydroxy nitrosamines was discovered in our laboratory during the attempted saponification of the β-acetoxy nitrosamine 1 (R = Ac; eq 2) in alcoholic KOH.[1,2] Our work also showed that



1, R = H or Ac

the corresponding alcohol (1, R = H) underwent this transformation, and it was our initial goal to determine the generality of this reaction for a wide range of structurally varied β-hydroxy nitrosamines. We have given several preliminary accounts of this work at various stages.[1,2,10-12]

The substrates of interest (Chart I) are all known compounds and were either prepared by the Seebach and Enders condensation of the appropriate aldehyde or ketone with the α-lithio nitrosamine[15-18] or by the nitrosation of the corresponding β-hydroxy amine. Details regarding the synthesis and characterization of the substrates employed in this work were equilibrium mixtures of the *Z* and *E* (syn and anti) isomers.

As our research on the fragmentation reaction evolved, it became clear that reactivity not only was highly dependant on structure but also was significantly influenced by base strength and concentration. In order to ensure sufficient reactivity in comparative kinetic studies, we developed several typical reaction conditions.

Generally, the substrate of interest was heated at 50 or 70 °C in either THF (tetrahydrofuran) containing a small portion of *t*-butyl alcohol (*t*-BuOH) or in *t*-BuOH with the desired quantity of KO-*t*-Bu (potassium *tert*-butoxide). In several cases other base/solvent systems were utilized. After a predetermined time an aliquot of the reaction mixture was quenched with either acetic or phosphoric acid and subjected to thin-layer and GLC or HPLC chromatographic analysis. By utilization of the Griess reagent it is possible to determine the number of nitrosamine products in the reaction mixture. Quantitation was then performed by HPLC or GLC by using authentic compounds as standards. For the most part, reaction products were identified by mass spectrometry after chromatographic separation. This method is particularly valuable when one is working with potentially dangerous materials such as carcinogenic nitrosamines.

All of the β-hydroxy nitrosamines shown in Table I have been found to undergo the fragmentation reaction described by eq 1. From the nitrosamine product perspective

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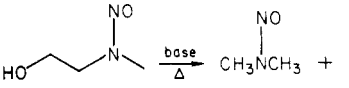
the majority of reactions are very clean. Only the (β-hydroxyethyl)nitrosamines **2** and **3** gave nitrosamine products in addition to the simple fragmentation product (eq 3 and 4). Treatment of **2** with 1:1 sodium ethoxide/ethanol in dry THF under N_2 at reflux for 24 h gave starting material, the vinylnitrosamine **12**, and the cleavage product, dimethylnitrosamine (**11**). This transformation and the more complex one shown in eq 4 are kinetically complicated, and the characterization of these processes as well as a mechanism for vinylnitrosamine production from these substrates is the subject of a forthcoming paper from our group.[19] The relative product yields depend upon the conditions, but the yield of cleavage product (**11** from **2** and **2** from **3**) is small (less than 15%) in both cases. It is significant that these β-hydroxy nitrosamines are the only ones we have observed to give vinylnitrosamines.

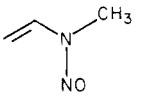
The strongly basic conditions under which the cleavage reaction is observed is, of course, destructive to most of the carbonyl products, and attempts were made to characterize them in only several instances. Benzophenone survives the reaction conditions well and is isolated from the fragmentation of **9**. In like manner benzaldehyde can be isolated from the base-induced cleavage of **7**, but it undergoes a subsequent Cannizzaro reaction to give benzyl alcohol and benzoate (in alcoholic KOH). Although the rate of the Cannizzaro reaction is reduced with KO-*t*-Bu, it does proceed and either gives rise to the consumption of base (via benzoate) or produces a much more acidic alcohol. As a result the use of substantially more than a catalytic amount of base is required in order to avoid a departure from pseudo-first-order kinetics.

The production of enolizable carbonyl compounds in the strongly basic cleavage reaction medium produces a similar set of problems. Reaction products from the treatment of **5** with KOH in ethanol were analyzed by GC/MS. In addition to dimethylnitrosamine and butanal, several secondary reaction products of the latter compound were found. These included the aldol condensation product 2-ethyl-2-hexenal and butanol (formed by a Cannizzaro reaction?). Aldol condensation followed by dehydration can result in the conversion of strong base into weaker hydroxide. Thus the carbonyl product of the reaction can act to inhibit further cleavage.

Our principal aim in this study is to elucidate the factors which affect reactivity, and we therefore made no attempt to maximize reaction yields. Nevertheless several experiments show that good yields of fragment nitrosamines can be obtained. The reaction of (2-hydroxy-2,2-diphenylethyl)methylnitrosamine (**9**, 0.25 M) in 95% ethanol with 2 M potassium hydroxide produced a nearly quantitative yield of dimethylnitrosamine after 15 h of being heated at reflux. Very little dimethylnitrosamine was detected when lower concentrations of base were employed at 25 °C. Upon workup the reaction mixture yielded benzophenone and dimethylnitrosamine which were characterized spectroscopically. When **9** was treated in THF with KO-*t*-Bu containing *t*-BuOH at 70 °C, a 74% yield of dimethylnitrosamine was produced within 2 h. The yields of products obtained with this substrate **9** which produces a nonenolizable ketone suggest that the transformation is largely irreversible under the conditions employed here. Of course, the reaction shown in eq 1 is just the reverse of the elegant synthetic transformation developed by Seebach and Enders[15,16,18-22] (vide infra) and is, therefore, reversible. The observation of reversibility, however, is dependent on the reaction conditions and the consumption rates of the carbonyl products. The only cases of a reversible reaction which were detected with the substrates used in this work involved the complex reactions of (2-hydroxyethyl)methylnitrosamine (**2**) and *N*-nitrosodiethanolamine (NDELA, **3**; eq 3 and 4) where the carbonyl

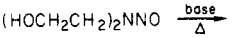


2 **11**



+ CH_2O + H_2O (3)

12



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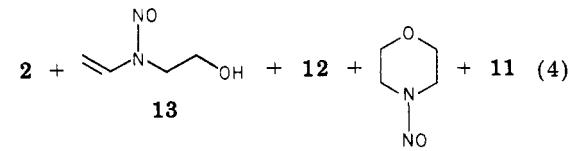

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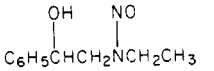
product is formaldehyde. Due to the complexity and unusual nature of these reactions this fact will be documented in a forthcoming paper.[19] Because of this, however, several experiments were performed with (2-hydroxypropyl)methylnitrosamine (**4**) to test for reversibility. The nitrosamine product DMN (**11**, 1.15 M) was heated at 70 °C with **4** (0.25 M) in *t*-BuOH containing 1 M KO-*t*-Bu. The substrate **4** disappeared, and DMN was formed at the normal rate. There was no indication of an approach to equilibrium given by the substrate or DMN vs. time data. The presence of DMN in the initial reaction mixture did not change the quantity formed from the substrate for the length of the experiment (90% consumption of substrate) or for any specific time (compared to no initial DMN). Sample calculations employing various values for the hypothetical equilibrium constant demonstrate that "*K*" for the fragmentation must be greater than 10 or a deviation from the observed rate constant would result. [The terms for the reversible case containing DMN and the simple first-order case differ by yS_0/K ($DMN_0 + yS_0$), where y is the fraction of reaction at t, $S_0 = 0.25$ M, and $DMN_0 = 1.15$ M.] Attempts to reverse this reaction by employing large concentrations of acetaldehyde in the cleavage reaction of **4** were not profitable because of its rapid base-catalyzed condensation.

In another experiment we looked for the formation of crossover products in the fragmentation of *N*-nitrosoephedrine with KO-*t*-Bu/*t*-BuOH (40 °C/7 days). GC/MS analysis of the product mixture confirmed the presence of ethylmethylnitrosamine, benzaldehyde, and unreacted *N*-nitrosoephedrine but none of the isomeric (2-hydroxy-2-phenylethyl)ethylnitrosamine (**15**, the crossover product) was detected.



15

Sodium borohydride was also used in several reactions to trap the aldehyde or ketone by reduction and prevent

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Table II. Rate Constants for the Fragmentation of 7 vs. [KO-t-Bu]

entry	$10^7 k_{obsd}$, s^{-1} [a,b]	[KO-t-Bu], M
1	5.45	0.49
2	3.20	0.14
3	2.50	0.07
4	1.56	0.044

[a] Plot of k_{obsd}^{-1} vs. $[RO^-]^{-1}$ gives a slope = 4.6 ± 0.5 × 10^{-6} s^{-1} and an intercept = −6.16 ± 2 (r = 0.988); this gives K = 66 and k = 7.5 × 10^{-7} s^{-1}. [b] In t-BuOH at 35 °C.

Table III. Rate Constants for the Fragmentation of 6 vs. [KO-t-Bu]

entry	$10^6 k_{obsd}$, s^{-1} [a,b]	[KO-t-Bu], M
1	2.31	0.12
2	6.74	0.265
3	10.4	0.38
4	15.3	0.50

[a] Plot of k_{obsd}^{-1} vs. $[RO^-]^{-1}$ gives a slope of 1.75 ± 0.06 × 10^{-5} s^{-1} and an intercept of 0.98 ± 0.14 (r = 0.9988). This gives kK = 1.87 ± 0.06 × 10^{-4} s^{-1}. [b] In t-BuOH at 50 °C.

the reverse reaction. This procedure did not result in rate or yield changes, but we have some question about its effectiveness because of our subsequent experience with substrates 2 and 3.

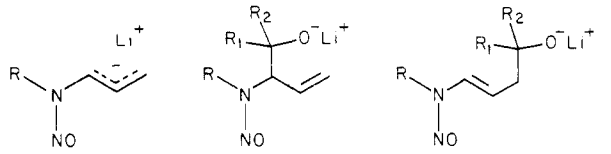
The kinetics of the reaction were followed by monitoring the concentration of substrate or fragment nitrosamine (usually both were followed) as a function of time by HPLC or GLC. Concentrations were determined by using standard curves, and details are given in the Experimental Section. Kinetic studies were done either in tetrahydrofuran containing 1 equiv of t-BuOH/equiv of KO-t-Bu or in t-BuOH with KO-t-Bu as the base. Except for substrates 2 and 3, the reactions were kinetically well-behaved. The rate of substrate disappearance was equal to the rate of fragment nitrosamine appearance. Plots of ln [substrate] or ln [S_0 − (fragment nitrosamine)] vs. time were linear throughout this period as is demonstrated by the data in the Experimental Section. The observed rate constants were obtained by linear regression analysis and are reported in Table I. Repetition of the experiments under the same conditions gave reproducible rate constants.

As was anticipated, the reaction rate was a function of both the solvent and the concentration of the base. The effect of base concentration on the reaction rate was evaluated for substrates 7 and 6 and is reported in Tables II and III, respectively. Plots of $1/k_{obsd}$ and $1/[RO^-]$ were linear. The parameters obtained from these plots are given in the footnotes to Tables II and III. For the same substrate at the same base concentration and temperatures the reactions conducted in THF were more rapid than those carried out in t-BuOH. As the concentration of t-BuOH in the THF was increased, the rate of the reaction decreased (see Table I entries 13 and 14).

Discussion

Prior to and during the course of our research publications from the Seebach group on the synthetic utility of the α-nitrosamino carbanion began to appear in the literature.[15-18,20-25] A brief and pertinent review of this work in relation to ours is worth while. Keefer and Fodor[26] were the first to demonstrate the unusual acidity of the carbon-bound hydrogens adjacent to the nitrosamine functionality by both base-induced deuterium exchange and alkylation of the α-nitrosamino carbanion. Seebach's group, however, has reported on the full synthetic utility of the α-nitrosamino carbanion. Of particular interest to the work reported here is their demonstration that β-hydroxy nitrosamines could easily be produced in high yields by the ionization of the nitrosamine α-hydrogens with lithium disopropylamide (LDA) at −78 °C followed by the introduction of an aldehyde or ketone and neutralization at −78 °C with glacial acetic acid.[15-18] This transformation is essentially the reverse of the one shown in eq 1. Further work by the Seebach group on the stereo- and regiochemistry of this reaction produced evidence of its reversibility.

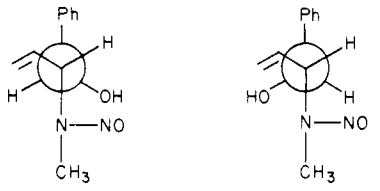
Specifically, Seebach and co-workers examined the condensation of [(tert-butylnitrosamino)allyl]lithium (16)



16 17 18

R = t-Bu

with either cyclohexanone or benzaldehyde as a function of time and temperature.[21] In the case of cyclohexanone the α adduct 17 was formed at low temperatures whereas the γ adduct 18 was the primary product at higher temperatures. The reversible nature of the condensation was proven by demonstrating the conversion 17 to 18 under the higher temperature reaction conditions. Similar results were observed with several other aldehydes and ketones. The Seebach group also demonstrated that the addition of benzaldehyde to 16 (R = CH_3) gave rise to a threo–erythro 19 + 20 product mixture at low temperatures and



19 20

short times. Under the conditions of the reaction, reversible condensation converted 20 to the more stable threo form 19 at higher temperatures.

In another paper, the problem of the regio- and stereoselectivity of "hydroxylation" of three methyl-substituted N-nitrosopiperdines is considered by the Seebach group.[22] Here the authors encounter the problem that the deuteration and benzophenone condensation of the lithio derivatives of these compounds do not give the same regio- or stereochemistry in each case. One of the explanations offered for this phenomenon is the possible reversible condensation of benzophenone with an equilibrating nitrosamino carbanion. Experimental evidence is given in support of this hypotheses. In another paper the Seebach group considers the relative merits of potassium or lithium derivatives of nitrosamines in their now familiar synthetic scheme.[23] In an extension of the limited work of Walser and Silverman,[27] KO-t-Bu is used to effect the condensa-

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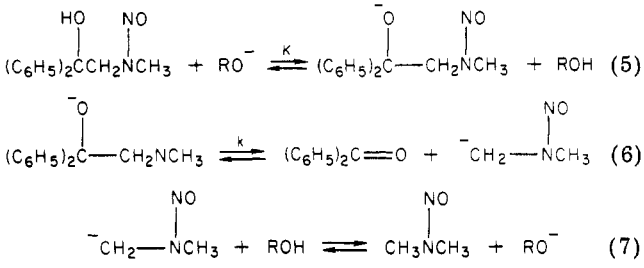
(27) Walser, A.; Silverman, G. *J. Heterocycl. Chem.* **1973**, *10*, 883.

tion of a ketone and an appropriate nitrosamine in what the authors describe as in situ generation of the nitrosamine carbanion. In one case, *tert*-butylmethylnitrosamine does not yield the appropriate adduct with benzophenone whereas use of LDA gave a 67% yield. This fact and the lower yields generated by the in situ method are thought by the authors to arise from the different stabilities of the lithium and potassium alkoxide adducts toward reversion.

From the perspective of our work the explanations of the Seebach group seem very plausible. Considering the relative ease of some of the fragmentations, particularly those which give ketones, it is perhaps surprising that reversibility has not played a larger role in determining yields, stereochemistry, and regiochemistry. On the other hand, from the perspective of Seebach's synthetic transformation, the relative ease of these fragmentations and our inability to demonstrate significant reversibility (except with compounds **2** and **3**) may appear striking. Obviously the consumption of the aldehyde or ketone product by either aldol condensation coupled to subsequent dehydration or Cannizzaro disproportionation (to alcohols and carboxylates) drives the reaction in the fragmentation direction. An assumed feature of this fragmentation/condensation reaction pair, which is common to all such transformations, is the large positive entropy of reaction associated with the greater degrees of freedom gained by the conversion of one molecule into two. In most of the cases studied here it is obvious that ΔH is small enough to permit the $T\Delta S$ term to change the sign of ΔG between −78 and +35 °C (for **9**). At low temperatures $T\Delta S$ is small and condensation is favored. The magnitude of $T\Delta S$ increases with T so that the resulting equilibrium constant becomes greater than one, and fragmentation is favored. While precise quantitative data cannot be given at this point to support this argument, the reversible condensation–fragmentations of benzophenone, DMN, and **9** are under study in our laboratory, and condensation in THF containing *t*-BuOH is found at −78 °C, but fragmentation is 99% complete at 0 °C.

A simple mechanistic hypothesis for the fragmentation reaction is given in eq 5–7 for compound **9**. Equation 1



(5)

(6)

(7)

is the sum of eq 5–7 and is expected to truly express the equilibrium if the base is present in catalytic amounts and if its conjugate acid has an acidity comparable to that of the substrate alcohol. Under the conditions employed by the Seebach group the equilibrium is best expressed by eq 6. The α-nitrosamino carbanion is produced essentially irreversibly by using a very strong base (LDA). After the carbanion is generated in aprotic media (THF), it is cooled to −78 °C, and condensation takes place. The neutralization of all bases in the reaction mixture at this temperature prevents fragmentation, and yields are principally a function of the equilibrium position of eq 6 at −78 °C. In all of the reactions reported here the solvent contained some alcohol which shifts the carbanion protonation and the fragmentation to the right. Thus relatively high temperatures, protic solvents, and consumption of carbonyl products all favor the observation of the fragmentation.

The data of Tables II and III clearly demonstrate that the observed rate constants increase with increasing [*t*-BuO⁻]. Since the analytical concentration of the substrate $[SOH]_A$ is [SOH] + [SO⁻] at any time, the relationship between the k_{obsd} and k of eq 6 is given by eq 8 where K

$$k_{obsd} = k\left(\frac{K[RO^-]}{K[RO^-] + K[ROH]}\right) \quad (8)$$

is the equilibrium constant of eq 5 and [RO⁻] and [ROH] are the respective concentrations of *t*-BuO⁻ and *t*-BuOH. The rearrangement of eq 8 gives eq 9 in a form suitable

$$\frac{[ROH]}{[RO^-]} = \frac{Kk}{k_{obsd}} - K \quad (9)$$

for the determination of k and K, providing K is significantly greater than unity. A reciprocal plot of the data in Table II for the fragmentation of (2-hydroxy-2-phenylethyl)methylnitrosamine (**7**) in *t*-BuOH at 35 °C gave $K = 66$ and $k = 7.5 \times 10^{-7}$ s⁻¹. We have estimated $K \approx 100$ by calculating a Taft σ^* of 0.91 for $CH_3N(NO)CH_2$ (CH_3, $\sigma^* = 0$) by employing literature data for the acidity of *N*-methyl-*N*-nitrosoglycine (*N*-nitrososarcosine)[28] and using literature data for the acidity of alcohols.[29-31] The fact that **7** is significantly more acidic than *t*-BuOH means that relatively high base to substrate ratios are useless for determining K and k by eq 9 because such ratios guarantee almost complete ionization of the substrate alcohol. Evidence of this effect is particularly noticeable in THF where an increase in [*t*-BuO⁻] did not produce an increase in k_{obsd} (see Table I runs 19 and 20).

In the case of the tertiary nitrosamino alcohol (2-hydroxy-2-methylpropyl)methylnitrosamine (**6**), the uncertainty and near zero value of the intercept obtained from a plot of the data in Table III according to eq 9 did not permit separate determinations of k and K. The value of kK at 50 °C is $1.87 \pm 0.06 \times 10^{-4}$ s⁻¹. Using Taft parameters, we have estimated $K \approx 20$ for the alcohol **6**. Our data would suggest a value smaller than this, but it is reasonable that it should be more acidic than *t*-BuOH due to the electron-withdrawing effect of the methylnitrosamino function.

The data of Table I show that the fragmentation reaction is more rapid in THF than it is in *t*-BuOH (Table I, runs 8 and 10, 12 and 15). This phenomenon is certainly in accord with predictions of eq 9 and is particularly well demonstrated by the fragmentation rate constants determined from runs 13 and 14 for the fragmentations of **6** in THF containing 0.03 and 0.003M *t*-BuOH, respectively. The tenfold reduction in alcohol concentration produced a 84-fold increase in rate in this case. The fragmentation rate of **6** was also determined in the superior cation solvating solvent HMPA (run 16), but k_{obsd} fails to reveal any striking effect since it is intermediary between the constants of runs 13 and 14.

The reactivity differences displayed in Table I are not in agreement with alcohol acidity being a primary determinant of reactivity. The tertiary nitrosamino alcohols fragment much more rapidly than the primary alcohols. The reactivity differences therefore stem from some other source although relative substrate acidity plays a role as demonstrated in Tables II and III.

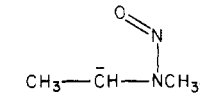
Our primary goal in this research is to discover how structural change affects reactivity. It is important to note

(28) Lijinsky, W.; Keefer, L.; Loo, J. *Tetrahedron* **1970**, *26*, 5137.
(29) Hine, J.; Hine, M. *J. Am. Chem. Soc.* **1952**, *74*, 5266.
(30) Taft, R. W. *J. Am. Chem. Soc.* **1953**, *75*, 3120.
(31) Ballinger, R.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795.

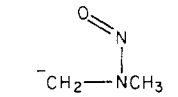
at the outset of this discussion that we have discovered that the orientation of the N–NO group (syn or anti to the hydroxyl-bearing carbon) plays a major role in determining the propensity of the β-nitrosamino alcohol toward cleavage. The syn isomer of **9** (*Z*) fragments much more rapidly than the anti one (*E*), and this is discussed in the following papers.[32,33] This phenomenon has also been documented for **7** and several similar compounds although the stereoelectronic effect is much more dramatic with **9**. The ΔG value for the interconversion of the syn [(*Z*)-**9**] and anti [(*E*)-**9**] isomers of **9** is 23.6 kcal/mol and our experimental data support the hypothesis that (*E*)-**9** must isomerize to (*Z*)-**9** before fragmentation occurs. We believe this is characteristic of all of the fragmentation reactions reported here as well. Since the equilibrium syn–anti isomer ratio is determined by the steric bulk of the groups attached to N, all of the compounds studied here exist in at least 75% anti (*E*) form at 25 °C because they are all methylnitrosamines (except for NDElA which is symmetrical). Thus, the interpretation of structural effects on the cleavage rate is complicated by two factors. (1) The kinetics were performed on *Z*–*E* mixtures, and the major isomer is the less reactive. (2) The base-independent rate constants have not been determined for all substrates. Despite these limitations structural effects can be discerned by pairwise comparison of the rate constants where measurements were made under the same or very similar conditions. Since the types of structural changes made here are not expected to significantly change the *Z*–*E* isomerization rate or equilibrium constants, the majority of the observed rate constants should be a function of k (eq 6) and K (eq 5) (or the two rate constants which compose K). If the fragmentation of eq 6 is much more rapid than the *Z*–*E* isomerization then k_{obsd} will depend only on the conversion rate of the *E* isomer to its *Z* form (steady state for *Z*). The only compound which *may* behave in this manner is **9**.

The data of Table I reveal a relationship between the fragmentation rate and the thermodynamic stability of the incipient carbonyl product. The primary and secondary nitrosamino alcohols which generate aldehydes upon fragmentation undergo cleavage more slowly than the tertiary nitrosamino alcohols which produce ketones. It is well-known that simple ketones have lower heats of formation than their isomeric aldehydes. Moreover, one expects aldehyde stability to increase in the order formaldehyde < acetaldehyde < benzaldehyde. Similarly, benzophenone, because of the conjugation of the carbonyl, should be "more stable" than acetone.

Substrate **2** which produces formaldehyde is cleaved more slowly than **4** which gives acetaldehyde. In fact, our kinetic analysis of the fragmentation of (2-hydroxyethyl)methylnitrosamine (**2**) suggests that the reported rate constants are for the *Z* isomer only[19] whereas those for **4** are for the *Z* + *E* mixture, and the rate difference between these substrates may be even greater. A similar comparison of the rate constants for the reactions of **4** and **7**, of **6** and **9**, and **7** substantiates the reactivity order **9** > **6** > **7** > **4** > **2**. Thus the relative rates of fragmentation parallel the "stability" of the incipient carbonyl product. These findings support the hypothesis that the fragmentation step (eq 6) is endothermic and that the transition-state structures resembles product structure. If this is true, the reaction rate will also be a function of the nitrosamino carbanion stability. A comparison of runs 18 and 21, which were carried out under parallel conditions, supports this idea. The carbanion produced from fragmentation of *N*-nitrosoephedrine (**8**) is **21** and will be less stable than



21



22

22 produced from **7** due to the inductive effect of the methyl group. Benzaldehyde is the carbonyl product produced by both fragmentations.

Another interpretation of the rate data is suggested by a comparison of the fragmentation rates for (2-hydroxypropyl)methylnitrosamine (**4**) and (2-hydroxypentyl)methylnitrosamine (**5**) (runs 7 and 10). Kinetic runs under parallel conditions surprisingly show the larger molecule **5** to fragment 3.4 times more rapidly than **4**. Because we anticipated similar stabilities for their respective products ethanal and butanal, we repeated this experiment several times and obtained the same results. Since the fragmentation converts the OH-bearing carbon from tetrahedral to trigonal, the accompanying angle expansion can relieve strain in the ground state of **5** relative to that for **4**. If the transition-state energies for cleavage of **4** and **5** are approximately equal, **5** will have the lower activation energy for cleavage because of its higher ground-state energy. This hypothesis could be used to rationalize all of the observed reactivity difference except the **7**–**8** pair. If the major factor which determines relative rates is "relief of ground-state steric strain", then **8** should fragment more rapidly than **7**, but it does not. A cursory determination of the rate constant for the fragmentation of (2-hydroxy-2-methyl-2-phenylethyl)methylnitrosamine (**10**) in *t*-BuOH containing 0.29 M KO-*t*-Bu at 50 °C produced a value of 56×10^{-6} s^{-1}. This value (resulting from only a single determination) is slightly higher than that from the benzophenone-producing compound **9** (see run 22). Our estimates of alcohol acidity show **9** to be approximately four times more acidic than **10**. Thus the greater reactivity of **10**, if true, is out of place. From the perspective of steric effects, **9** should react much more rapidly than **10** due to the greater bulk of two phenyl groups compared to a phenyl and a methyl. The same reactivity difference is predicted if carbonyl group stability significantly influences reactivity. The group ΔH_f values of Benson's group[34] for various substituted carbonyls provide an index of thermodynamic stability and should be related to transition-state energies where a carbonyl group is produced in an endothermic process. The group ΔH_f values for the carbonyl compounds of interest are as follows: H_2CO, –27.7; H–CO–C, –29.6; $(C)_2CO$, –31,5; HCO–Ar, 31.7; Ar–CO–C, –37.6; Ar_2CO, –39.1. The difference in these values is presumably related to electronic factors. Alkyl groups stabilize the electron-deficient carbonyl carbon through induction, and aromatic groups do so by resonance. The Benson values show little difference between an aromatic aldehyde and an aliphatic ketone. Comparison of runs 15

(32) Loeppky, R. N.; Hazlitt, L. G. *J. Org. Chem.*, following paper in this issue.
(33) Loeppky, R. N.; Outram, J. R.; McAllister, J.; Lopatin, E., submitted for publication in *J. Org. Chem.*
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(39) Hatt, H. In "Organic Syntheses"; Blatt, A. H., Ed.; Wiley: New York, 1943; Colect. Vol. II, p 211.

and 17 (Table I) reveals that the acetone-producing **6** reacts slightly faster than benzaldehyde-producing **7**. Since **6** is more acidic than **7**, it is very likely that steric factors contribute to the greater reactivity of **7**. As a result of these considerations we believe that both steric and electronic factors contribute significantly to the structure–reactivity profile for these fragmentations. None of the substrates examined provides an adequate determination of their relative contributions. Idealy we should make reactivity comparisons by using base and equilibrium constant independent rate constants from the fragmentation of the *Z* isomers. This must await further experimentation.

An alternative view of the mechanism of these reactions comes from Seebach's group[22] and is given in Scheme I. In this case the substrate alkoxide ion undergoes homolytic fission of the C_α–C_β bond to give a ketyl (anion radical) and α-nitrosamino carbon centered radical species (the chemistry of which appears to be unknown). This radical pair undergoes electron exchange to generate the carbonyl compound and the α-nitrosamino carbanion which captures a proton from the solvent. If the radical pair dissociates, a more complex chemistry is envisioned. On the other hand, if electron exchange between the radical pair is rapid, the mechanism is not significantly different from that given in eq 5–7. Seebach et al. have suggested the possible minor involvement of benzophenone ketyl in the condensation of an α-metalo nitrosamine with benzophenone.[22] They note the formation of a blue color which we have also seen on occasion in some of the fragmentations of **9**. At other times orange-red colors have been observed by us. Even though benzophenone ketyl is blue, complexation of this substance with DMN or another nitrosamine could produce a color change. While the process of Scheme I may be operative to some extent in our transformations, our data support the mechanism given in eq 5–7, and at this time we can offer little experimental support for this radical process.

Conclusion

The data presented herein demonstrate that the base-induced fragmentation of β-hydroxy nitrosamines is a general transformation (eq 1) occurring with primary, secondary, and tertiary nitrosamino alcohols. The secondary and tertiary alcohols cleanly give only a single nitrosamine product whereas the reaction of the primary alcohols is more complex. Both the reaction temperatures employed (35–70 °C) and the consumption of the carbonyl coproducts by the strong base favor fragmentation over condensation (reverse of the reaction). The reaction exhibits the characteristic of alkoxide catalysis and is most rapid in aprotic solvents. The reaction rate is a function of structure, and the nitrosamino alcohols are cleaved in the order tertiary > secondary > primary. As the stability of the incipient carbonyl and carbanion products increase, the reaction becomes more rapid. The reaction also appears to be influenced by relief of steric strain in the substrate. These observations and other work support the mechanistic hypothesis of eq 5–7 which involves rate-determining cleavage of the C_α–C_β bond, but the nitrosamine syn–anti isomerization rate is also important and is discussed in the following papers.[32,33] These results provide a basic chemical framework for understanding the possible role of β-hydroxy nitrosamines in environmental carcinogenesis.

Experimental Section

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

General Methods. In the course of this research several kinds of analytical chromatographic equipment were employed. These included a MicroTec 2000 R GC with an FID detector, a Varian Aerograph GC with a TC detector, a HP 5880 A Level 4 GC with FID and NPFID detectors, a homemade HPLC consisting of a Haskell air-driven pump (3000 psig maximum), a Rheodyne fixed-loop injector, the column, and an ISCO UV monitor (254 nm), and a Waters dual pump gradient HPLC employing a WISP autosampler and a UV detector (254 nm). The output from the first two GC's and the first HPLC was fed into a Columbia Scientific SRS 208 integrator which generated a printed output of peak area vs. retention time. Peak areas from the HP GC and the Waters HPLC were obtained through the HP 5880A Level 4 data treatment system. IR spectra were taken on a Perkin-Elmer 237B spectrometer. NMR spectra were obtained principally on a Varian EM360 instrument, and mass spectra were obtained from a Du Pont 292 mass spectrometer connected to a Varian GC. Melting and Boiling points are uncorrected. Chemicals, except those given below, were obtained from commercial sources and purified as necessary.

Preparation of Nitrosamines. All of the nitrosamines used in this work are known compounds and were prepared by literature methods. Appropriate documentation is provided in Table IV.

Product Characterization. Because of the carcinogenic nature of the substrates and products, the product mixtures were neutralized with glacial acetic acid or 2.5 M H_3PO_4 and analyzed by GC/MS. The mass spectra of all substances identified here have been published or were obtained from the authentic compounds with the exception of that of 2-ethyl-2-hexenal which was obtained from the fragmentation of **5** MS; *m/e* (relative intensity) 125 (39), 111 (23), 97 (51), 69 (22), 67 (22), 55 (100), 43 (32), 41 (69), 39 (32), 29 (22), 27 (22). We did not attempt to characterize all of the products arising from consumption of the carbonyl product. TLC on silica gel plates followed by application of the Griess reagent gave an indication of the number of nitrosamines in the product mixture. All "Griess positive" products were characterized. A typical procedure is as follows.

Fragmentation of (2-Hydroxyethyl)methylnitrosamine (2). (2-Hydroxyethyl)methylnitrosamine (**2**; 0.78 g, 7.5 mmol), *tert*-butyl alcohol (0.94 mL freshly distilled from $LiAlH_4$), and potassium *tert*-butoxide (1.12 g, 11 mmol) were disolved in freshly distilled dry THF (15 mL) and were stirred magnetically to effect dissolution in an inert atmosphere. Several 0.1-mL samples were taken, diluted with water, and titrated with standardized potassium hydrogen phthalate to determine the base concentration (0.66 M). The mixture was heated at reflux in the inert atmosphere for 72 h, cooled, and neutralized with 2.5 M H_3PO_4. TLC of this mixture on silica gel plates in petroleum ether F/methanol/methylene chloride (4:1:5) showed three "Griess positive" spots at R_f 0.41, 0.63, and 0.8. The neutralized mixture was diluted with a saturated solution of NaCl and extracted three times with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with saturated salt, dried over $MgSO_4$, and concentrated for GC/MS analysis by using a Porapak-PS $^1/_8$ in. × 2 ft column (120–240 °C; 20 °C/min). Comparison of the mass spectra with authentic materials permitted characterization of dimethylnitrosamine (t_R = 0.4 min), methylvinylnitrosamine (t_R = 0.6 min), and starting material **2** (t_R = 1.24 min).

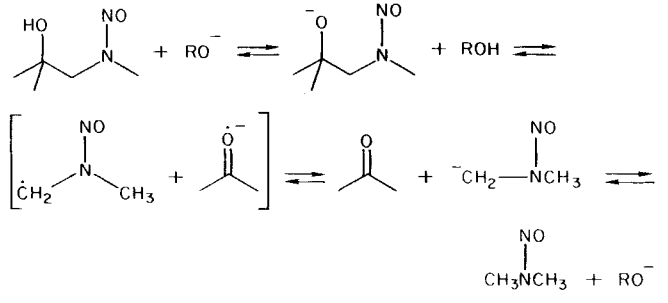
Kinetics Experiments. All kinetics experiments were conducted in Teflon-lined rubber-capped serum vials in a thermostated constant-temperature bath at the temperature (±0.1 °C) given in Tables I–III. Samples were removed by calibrated syringe and discharged into a neutralizing mixture for subsequent chromatographic analysis. In some instances dimethylnitrosamine was determined by GC using *p*-xylene as an internal standard. Three to four repetitive analyses were made for each point and concentrations were calculated from a standard curve. Standard mixtures (prepared by weight from chromatographically pure compounds) were used to check instrument calibration prior to each analysis. For the most part, HPLC analysis did not employ internal standards, as the fixed volume loop injector and the WISP injector are highly reproducible. Analysis precision was 0.5% or better. HPLC analysis employed reversed-phase ODS columns and methanol water eluents. Rate constants were determined from a plot of 5–15 data points (either ln *S* vs. *t* or ln (S_0 –

Table IV. Characterization and Preparation of Nitrosamines

name	no.	prep method	phys property found	phys property reported	ref	^{1}H NMR, δ
(2-hydroxyethyl)methylnitrosamine	2	*a*	bp 93–96 °C (0.05 torr)	bp 110–111 °C (1 torr)	35	[e] *E*: 3.73 (s, 3, CH_3), 3.93 (t, 2, CH_2), 4.00 (t, 2, CH_2-O). *Z* 3.10 (s, 3, CH_3), 4.16 (t, 2, CH_2-O), 4.23 (t, 2, CH_2), 3.85 (s, 1, OH)
N-nitrosodiethanolamine (bis(2-hydroxyethyl)nitrosamine	3	*a*	MS (see ref 12)	MS (see ref 7)	36	[f] 3.16 (t, 2, CH_2Z), 3.40 (m, 4, CH_2-O), 3.9 2, CH_2 *E*), 3.85 (br, 2, OH)
(2-hydroxypropyl)methylnitrosamine	4	*b*	bp 101–103 °C (1.5 torr)	bp 110–112 °C (1 torr)	37	[e] *E*: 1.34 (d, 3, CH_3), 3.16 (s, 3, NCH_3), 4.13 (m, 2, CH_2). *Z*: 1.2 (d, 3, CH_3), 3.66 (m, 2, CH_2), 3.86 (s, 3, NCH_3), 4.43 (s, 1, OH)
(2-hydroxypentyl)methylnitrosamine	5	*b*	bp 110 °C (1.4 torr)	120 °C (1 torr)	17	[e] 1.0 (t, 3, CH_3), 1.5 (m, 4, $(CH_2)_2$), 3.2 (s, 3, NCH_3E), 4.0 (s, 3, NCH_3 *Z*), 4.3 (m, 1, CH), 3.75 (br, 1, OH)
(2-hydroxy-2-methylpropyl)methylnitrosamine	6	*b*	bp 58–61 °C (0.17 torr)	85 °C (0.3 torr)	17	[e] *E*: 1.3 (s, 6, CH_3), 3.2 (s, 3, NCH_3), 4.15 (s, 2, CH_2). *Z*: 1.18 (s, 6, CH_3), 3.72 (s, 3, N-CH_2), 3.93 (s, 2, CH_2), 2.65 (OH)
(2-hydroxy-2-phenylethyl)methylnitrosamine	7	*b*	mp 77 °C	73 °C	17	[e] *E*: 3.05 (s, 3, CH_3), 4.3 (d, 2, CH_2), 5.1 (t, 1, OH). *Z*: 3.70 (s, 3, CH_3), 3.85 (d, 2, CH_2), 5.05 (dd, 1, CH), 4.32 (s, 1, OH), 7.35 (s, 5, ArH)
(1*R*,2*S*)-*N*-nitrosoephedrine [[(1*R*,2*S*)-2-hydroxy-1-methyl 2-phenylethyl]methylnitrosamine]	8	*a*	mp 91–92 °C, $[\alpha]^{25}_D$ 225.8°	93 °C	38	[e] 1.39 (d, 3, CH_3), 2.89 (s, 3, NCH_3), 3.6 (m, 1, CH), 4.46–5.06 (m, 1, HC-O), 7.29 (s, 5, Ar H)
(2-hydroxy-2,2-diphenylethyl)methylnitrosamine	9	*b*	mp 113.5 °C	113.5 °C	17	[e] *E*: 3.00 (s, 3, CH_3), 5.02 (s, 2, CH_2). *Z*: 3.43 (s, 3, CH_3), 4.62 (s, 2, CH_2), 7.65 (m, 10, Ar H) 6.2 (s, 1, OH)
dimethylnitrosamine	11	*a*	bp 147 °C (745 torr)	149–150 °C (755 torr)	39	[e] 3.05 (s, 3, *Z* CH_3), 3.80 (s, 3, *E* CH_3)
ethylmethylnitrosamine		*d*	bp 92 °C (40 torr)	bp 80 °C (30 torr)	17	[e] *E*: 1.4 (t, 3, CH_3), 3.1 (s, 3, NCH_3), 4.2 (q, 2, CH_2). *Z*: 1.1 (t, 3, CH_3), 3.75 (s, 3, NCH_3), 3.55 (q, 2, CH_2).
methylvinylnitrosamine	12	*c*	bp 38 °C (22 torr)	bp 50–52 °C (30 torr)	35	[g] *E*: 3.27 (s, 3, CH_3). *Z*: 4.1 (s, 3, CH_3). 4.6–5.1 (m, 2, $=CH_2$), 8.27 (dd, 1, CH=).

[a] Prepared by amine nitrosation in acid. [b] Prepared by condensation of the lithionitrosamine with aldehyde or ketone. [c] Prepared by dehydrohalogenation of β-chloronitrosamine. [d] Prepared by methylation of the lithionitrosamine. [e] In $CDCl_3$. [f] In $(CD_3)_2CO$. [g] In CCl_4.

Scheme I



[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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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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