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(*E*)-2-Butanediazoic Acid Decomposes via a Diazonium Ion Intermediate†

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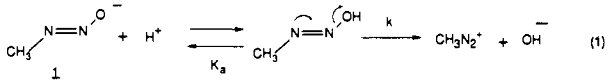
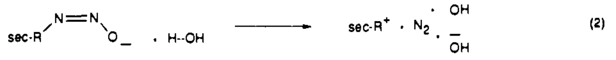
Alkane diazoates are reactive intermediates that are believed to be central to the DNA alkylating activity of a large number of carcinogens and cancer chemotherapeutic agents that contain the *N*-alkyl-*N*-nitroso functionality.[1] The diazoic acid forms are proposed to be intermediates in the nitrous acid-stimulated deamination of alkane amines,[2] and the related diazoic acid esters are purported intermediates in the deaminative rearrangements of nitrosamides.[3] Isomeric syn (*Z*) and anti (*E*) forms have been prepared by separate routes in organic media[4] but are generally unstable in aqueous media, decomposing with the evolution of nitrogen gas, and the syn forms are reported to be more reactive than the identically substituted anti forms.[5] It was recently concluded that the mechanism of decomposition of the (*E*)-methanediazoate (**1**) involves unassisted N–O bond cleavage of the diazoic acid as in eq 1,[6] but the mechanism of decomposition of the higher alkanediazoates remains a source of controversy. The data from a combination of product stereochemical and product solvent isotope incorporation analyses of the decomposition of chiral secondary syn alkane diazoates were rationalized according to the "ion-triplet" mechanism of eq 2.[7] Secondary diazonium ions have been considered insufficiently stable to exist as intermediates, and the concerted mechanism of eq 3 for the nitrous acid-stimulated decomposition of amines has been considered most likely by some.[8,9] The stepwise mechanism of eq 4 is favored by others on the basis of the products derived, mostly in organic media, from diazoester intermediates in nitroamide and nitrosamide decomposition.[11] Still others consider the matter open.[12] We report here the first direct kinetic analysis of the decomposition of a pair of secondary anti alkanediazoates (**2** and **3**) in aqueous media and deduce that the rate-limiting step for decomposition of the 2-butyl compound involves formation of the secondary diazonium ion from the diazoic acid, in accord with the mechanism of eq 4.



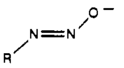
(1)



(2)

$$\text{sec-R{-}N{=}N{-}OH} \longrightarrow \text{sec-R}^{+} \cdot \text{N}_2 \cdot \overline{\text{O}}\text{H} \qquad (3)$$

$$\text{sec-R{-}}\overset{+}{\text{N}}{\equiv}\text{N} \cdot \text{OH}^{-} \longrightarrow \text{sec-R}^{+} \cdot \text{N}_2 \cdot \overline{\text{O}}\text{H} \qquad (4)$$



2, R = 2-butyl
3, R = 1-phenylethyl

Analytically pure diazoates **2** and **3** were synthesized by the procedure previously reported.[5,13] Decomposition of **3** in water and **2** in D_2O gave nearly quantitative yields of the expected alcohols and/or alkenes.[14] Decomposition kinetics were studied by mixing one part of a solution of basic 2-propanol containing the diazoate with 25 parts of an aqueous reaction mixture in a stopped-flow spectrophotometer and monitoring, at the ultraviolet maxima of 225 and 230 nm for **2** and **3**, respectively, the clean first-order decay of absorbance for 4–5 half-lives. The first-order rate constants k_{obs} increase by less than 5% with increases in buffer concentration, from 0.05 to 0.2 M, at a constant buffer ratio for buffers including acetate, phosphate, primary amines, and hydrazine. The buffer-independent first-order rate constant for decay, k_0, was thus accurately obtained from the intercepts of plots of k_{obs} against buffer concentration.

The unit slopes at higher pH of plots of log k_0 against pH, illustrated in Figure 1, indicate that protonated forms of the diazoates **2** and **3** are involved in the rate-limiting step for decomposition. This hydrogen ion dependence rules out the pH-independent ion-triplet mechanism of eq 2.[15] The absence of an effect of increasing buffer concentration on the value of k_{obs} in experiments with highly nucleophilic buffers, such as hydrazine, and the larger limiting rate constants for the decomposition of **2** and **3** compared to the methyl compound **1** exclude a number of mechanisms,[6] leaving fragmentation of the anti diazoic acid, eq 1, as the only reasonable alternative. Good fits, solid lines in Figure 1, to the steady-state rate equation for the mechanism of eq 1 are obtained using the values of pK_a = 8.83 and k = 96 s^{-1} for **2** and pK_a = 8.32 and k = 6.2 s^{-1} for **3**.

A comparison of the rate constants for decomposition of the diazoic acids of **2** and **3** indicate that the mechanism of decomposition of the 2-butyl compound involves formation of the

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(9) There is good evidence that product formation involves nucleophilic attack on primary diazonium ions that are presumably formed as in eq 1 from the diazoic acids in the nitrous acid-stimulated deamination of primary amines.[10] However, the possibility of a concerted formation of a primary carbocation, bypassing the diazonium ion, has been suggested, see ref 12, Gold et. al.

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(13) For **2** ($C_4H_9N_2ONa$). Anal. Calcd: C, 38.71; H, 7.31; N, 22.57. Found: C, 38.51; H, 7.22; N, 22.46. For **3** ($C_8H_9N_2ONa$). Anal. Calcd: 55.81; H, 5.27; N, 16.27. Found: C, 55.60; H, 5.30; N, 16.10.

(14) Decomposition of **2** in D_2O containing 0.01 M KOD (ionic strength 1 M $NaClO_4$) under a column of $CDCl_3$ containing the internal standard 1,4-di-*tert*-butylbenzene and analysis of the $CDCl_3$ by ^1H NMR gave yields of 7% 1-butene and 32% 2-butenes. Gas chromatography of decompositions carried out in the absence of a $CDCl_3$ phase gave a 53% yield of 2-butanol. Analysis by HPLC of decomposition products from **3** gave a 99.1% yield of 1-phenethyl alcohol and 0.9% styrene. All yields are based on the mass of the starting material.

(15) The ion-triplet mechanism is still viable in the case of the more reactive syn compounds for which it was posited.

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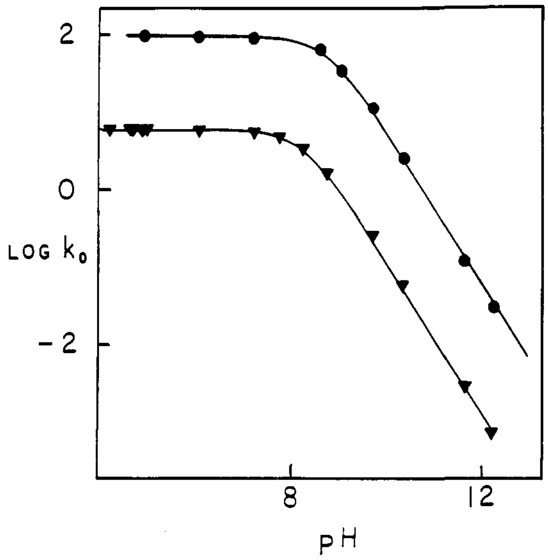

Figure 1. Plot of log k_0, the buffer-independent rate constant for decomposition, against pH for secondary alkanediazoates **2** (●) and **3** (▼) determined at 25 °C, ionic strength 1 M (NaClO$_4$), 4% 2-propanol.

diazonium ion, as in eq 4. If the anti 2-butanediazoic acid decomposed directly to the carbenium ion as in eq 3, the carbenium ion character in the transition state would be stabilized by the resonance interaction with the benzene ring in **3**. This would predict a larger value of k for the diazoic acid of **3** than for that of **2**. In contrast, the value of k is greater by a factor of 16 for the diazoic acid of **2** compared to **3**, which requires that there is no significant carbenium ion character in the transition state for the decomposition of the acid form of **2**. No conclusion is possible about the alternative mechanisms of eqs 3 and 4 in the case of compound **3**.

The 37-fold greater value of k for the diazoic acid of **2** compared to that of **1** represents a difference in activation energy of 2 kcal/mol and is consistent with the greater stability expected for the secondary diazonium ion compared to methanediazonium ion. Theoretical calculations indicate that substitution of a methyl or ethyl group for one hydrogen of the methanediazonium ion is stabilizing by 9 and 13 kcal/mol,[16,17] respectively, though this amount may be somewhat attenuated in the aqueous environment.

As regards the stability of a secondary diazonium ion toward nitrogen dissociation, a rough estimate suggests that it is likely thermodynamically favorable by 11 kcal/mol—or less in view of the expected attenuating solvent effect—on the basis of energetics in the gas phase and from theoretical calculations. Ethanediazonium ion dissociation is calculated to be exothermic by 11.5 kcal/mol.[17] While methyl-for-hydrogen substitution on the ethyl cation to give the secondary propyl cation stabilizes the carbocation by 27.5 kcal/mol,[18] a similar substitution also stabilizes the diazonium ion.[16,17] The net final value of -11 kcal/mol for dissociation of the 2-propanediazonium ion is based on the assumption that the fractional stabilization of the diazonium ion compared to the carbocation is the same as that for the ethane- and methanediazonium ion/carbocation pairs.[19]

We are presently undertaking a detailed analysis of the effects of diazoate structure on the decomposition chemistry of these important intermediates that will be described in future reports.

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(19) Recent calculations[17] indicate that substitution of a methyl group for hydrogen on the methanediazonium ion is destabilizing by 31 kcal/mol, which is 20% less than the carbocation stabilizing effect evident from the measured gas-phase hydride ion affinities[18] due to the countervailing stabilization of the diazonium ion.[16,17]