Ambident Ethyl N-Nitrosocarbamate Anion: Experimental and Computational Studies of Alkylation and Thermal Stability

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Abstract: Alkylation of N-nitrosourethane tetrabutylammonium salt (2-BuN) with four electrophiles (MeI, EtI, i-PrI, and PhCH2Br) was studied by 1H NMR in CD2Cl2 and CD3CN solutions. The ratio of the three regioisomers N-alkyl-N-nitrosourethane 3, azoxy 4, and O-alkylidiazotate 5 was practically independent of solvent but dependent on the nature of the electrophile. The anion 2 and O-alkyl derivative 5 are thermally unstable and decompose to ethyl carbamates 9 and 10, respectively, with a first-order rate constant (2-BuN): k = 18.5 ± 0.1 × 10^-5 s^-1; 5b (R = Et): k = 1.77 ± 0.02 × 10^-5 s^-1; 5d (R = PhCH2): k = 4.78 ± 0.08 × 10^-5 s^-1 at 35 °C in CD2Cl2. Further kinetic measurements gave activation parameters for the decomposition of 2 (Ea = 24.2 ± 0.3 kcal/mol and ln A = 30.9 ± 0.1). Gas-phase calculations at the MP2(fc)/6-31+G(d)//MP2(fc)/6-31G(d) level showed that the alkylation of 2 involves the lone electron pairs of the N-N-O atoms, and the calculated activation energies correspond well to the observed ratio of regioisomers 3-5. The theoretical analysis of the decomposition processes supports a concerted mechanism with a four-center transition state in the first step for all four compounds. The calculated activation energy order (2 < 5 < 3 < 4) is consistent with the observed order of stability. Decomposition of 2 and 5 is a unimolecular process, giving carbamates 9 and 10 in a single step. In contrast, rearrangement of 3 and 4 leads to alkyl diazonium ions. A detailed theoretical analysis indicates that the rate-determining step for thermal decomposition of 2 is the loss of molecular nitrogen, while in 5 it is the trans-cis isomerization process. The nonconcerted process involving homolytic cleavage of the O-N bond in 5 was found to be significantly less favorable.

Introduction

N-nitrosamines, N-nitrosocarbamates, and N-nitrosoureas are of considerable interest in synthetic chemistry, biochemistry, and medicine. They have been used as reagents,1-4 studied for their mutagenic and carcinogenic properties,5 and suggested as antitumor agents.6 Most of these studies have focused on the N-alkyl-N-nitroso derivatives, while much less attention has been paid to the properties and chemistry of secondary N-nitroso derivatives. Such compounds are generally less stable than the N-alkyl analogues but are formed equally easily from the -CONH2 derivatives under mild nitrosylation conditions.4 Unlike the tertiary N-alkyl derivatives, however, the secondary N-nitrosamines easily dissociate in aqueous solutions to form ambident anions.7 Surprisingly, the chemistry of such anions and their reactions with electrophiles has received little attention. During the past century, only a handful of secondary N-nitrosamines have been isolated and investigated. Perhaps the best studied among them is N-nitrosourethane 1.8 It has been established that 1 is more acidic than acetic acid,9 dissociates to form the anion 2, has limited stability in water and in the presence of amines,8,10 and forms a stable Pd complex.11 With the exception of a report9 on the formation of a silver salt 2-Ag and its reaction with MeI, no further investigations of 1 or its anion have been documented.

Anion 2 belongs to a relatively broad class of diazotates (anions derived from monosubstituted N-nitrosoureas), most

of which bear either an alkyl or an aryl substituent. Alkylation of these ambident anions is known to yield three possible products (Scheme 1) whose formation depends on the reaction conditions and the structure of the reactants. Generally, alkanediazotates react with alkyl electrophiles to yield the N-alkylated derivatives A,12,13 However, under highly polar aprotic conditions the corresponding azoxy compounds B were isolated in good yields,14,15 and the formation of significant quantities of unstable O-alkyl products C has been postulated.16 When a diazotate carries an aryl substituent, alkylation yields a mixture of isolable N- and O-alkylated products, A and C, but no formation of the azoxy regioisomer B has been reported.17,18 It has been demonstrated that the preference for O-alkylation increases in polar aprotic solvents and for more bulky alkyl halides.17,18 The exclusive formation of the O-alkylated product C has been reported for some N-aryl,19–22 and N-ethoxycarbonyldiazotates23,24 which promotes an SN1-type reaction and readily coordinates with the N-center.25 Simultaneous formation of all three regioisomers has never been observed directly in any of the diazotates.

Despite the numerous experimental results, there is no reported computational analysis for the alkylation of diazotates. This is in contrast with enolates, carbon analogues of diazotates, whose regiochemistry of alkylation and thermodynamic stability has been extensively studied experimentally26–28 and computationally.29–31 To our knowledge, there is also no theoretical work on the thermal decomposition of N-nitrosoamides or related compounds. This is particularly surprising since an enormous body of work involving mechanistic and carcinogenic studies of these compounds has accumulated over the past half a century.

Here we examine the alkylation of tetrabutylammonium ethoxycarbonyldiazotate (2-Bu4N+ with three alkyl iodides and benzyl bromide in aprotic solvents and study the formation of the three regioisomeric products 3–5 as a function of solvent polarity and steric demands of the electrophile (Scheme 2). The discussion of the observed regiochemistry of alkylation and thermal stabilities of anion 2 and products 3–5 is aided with extensive quantum-mechanical calculations of ground and transition state structures.

### Results

**Synthesis.** N-Nitrosourethane (1) was prepared according to a literature procedure8 by partial reduction of N-nitrourethane (6).32 The relatively unstable 1 was isolated as the silver salt 2-Ag+8 which was converted to the tetrabutylammonium salt 2-Bu4N+ (Scheme 3).

Azoxy ester 4b was prepared by oxidation of ethyl 2-ethylcarbazate (7) with m-chloroperbenzoic acid (mCPBA, Scheme 4). The ethylcarbazate 7 was obtained by borane reduction of ethyl 2-ethylidenecarbazate (8) according to a general procedure.33 Direct ethylation of ethyl carbazate with ethyl iodide or MeCHO/NaCN-BH3 in EtOH gave largely the diethyl derivative.

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**References**

(9) Hantsch, A.; Schümann, M.; Engler, A. Chem. Ber. 1899, 32, 1703–

(16) (a) Hantzsch, A.; Schumann, M.; Engler, A. Chem. Ber. 1899, 32, 1703–
     (b) M. J.; Luchter, K. M.; Mamantov, A. Chem. Ber. 1899, 32, 1703–
Reactions of 2-Bu$_4$N with Alkyl Halides. Reactions of tetrabutylammonium salt 2-Bu$_4$N with several alkyl iodides were conducted in two solvents of different polarity, CD$_2$Cl$_2$ and CD$_3$CN, at 0 °C or ambient temperature. The progress of the reactions and the rate of formation of products (Scheme 2) were monitored by $^1$H NMR. In all cases the A$_3$X$_2$ signal for the ethyl group of the starting material 2-Bu$_4$N and the characteristic signals for the alkyl halides were observed to diminish with a concomitant appearance of new, downfield-shifted sets of signals for the products. Reactions of 2-Bu$_4$N with methyl iodide and benzyl bromide, run at 0 °C, resulted in three clean sets of NMR signals. Analogous reactions with ethyl and isopropyl iodides were conducted at ambient temperature and resulted in a mixture of at least five compounds. NMR analysis revealed that two identical sets of A$_3$X$_2$ signals of at least five compounds. NMR analysis revealed that two identical sets of A$_3$X$_2$ signals were assigned to products of the thermal decomposition of the starting salt 2-Bu$_4$N (vide infra). An example of the NMR spectrum is shown in Figure 1a for the reaction of 2-Bu$_4$N with ethyl iodide.

The NMR signals (Table 1) were assigned to the three products shown in Scheme 2 based on matching intensities and coupling constants, general spectroscopic trends, literature reports for some derivatives, and differential thermal stability. Thus, the signals of the $\alpha$-hydrogens of the alkyl substituents in N-alkyl-N-nitroso carbamates were assigned to the three regioisomers with the signals of the $\alpha$-methylene group in the tetrabutylammonium cation (about 3.1 ppm). The ratios of N- to O-alkylation and azoxy to N-alkylated products were obtained by integration of the $\sim$COOCH$_2$CH$_3$ signals in the products as well as some characteristic peaks for the alkyl substituents. The results are listed in Table 2.

Further support for the assignments in Table 1 is provided by the difference in thermal stability of regioisomers 4 and 5. The reaction mixtures prepared in CH$_3$Cl were passed through a silica gel plug to remove the ammonium salts, redissolved in CD$_2$Cl$_2$, and thermolyzed at 35 °C for about 7 h. The low field set of signals that disappeared from the spectrum was assigned to the O-alkylated product, while those with ethyl and isopropyl iodides required ambient temperature to achieve appreciable reaction rates. At this temperature, however, thermal decomposition of 2-Bu$_4$N competes with the alkylation reaction. The observed qualitative differences in reactivity of the alkyl electrophiles are in good agreement with the general reactivities of alkyl halides with nucleophiles.

Stability of the Anion 2 and the O-Alkyl Derivatives 1. $^1$H NMR studies of the pure salt showed that anion 2 was cleanly converted into two new products over several hours at ambient temperature.

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Figure 1. Low field portion of NMR spectra of the reaction mixture of 2-Bu$_4$N with ethyl iodide in CD$_2$Cl$_2$: (a) spectrum of crude reaction mixture recorded after 105 min at 0 °C and then 20 min at 25 °C, (b) recorded after passing the crude reaction mixture through a SiO$_2$ plug, and (c) mixture shown in panel b after 430 min at 35 °C. Spectra recorded at 400 (panels a and c) and 300 MHz (panel b) instruments.
**Table 1.** Characteristic $^1$H NMR Chemical Shifts for Alkyl Halides and Observed Products in Alkylation of Ethyl N-Nitrosocarbamate Salt 2-Bu$_4$N$^+$

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<tr>
<th>R</th>
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<th>R-I</th>
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<th>N$\equiv$C=O</th>
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<th>N$\equiv$C=O</th>
<th>CH$_3$CH$_2$O-</th>
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<td>B</td>
<td>A</td>
<td>X</td>
<td>B</td>
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<td>X</td>
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<td>CD$_2$Cl$_2$</td>
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<td>1.37</td>
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<td>b 1.48</td>
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<td>4.37</td>
<td>4.59 and 1.56</td>
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<td></td>
<td>CDCl$_3$</td>
<td>e 1.46</td>
<td>4.56</td>
<td>4.93</td>
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<td>5.39</td>
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*The signals for the products were assigned based on matching intensities for multiplets and general trends in $^1$H NMR chemical shifts. The A$_1$X$_2$ signal of the ethyl group in the starting 2-Bu$_4$N$^+$ (CD$_2$Cl$_2$) $\delta$ 1.27 (t, $J$ = 7.1 Hz, 3H), 4.14 (q, $J$ = 7.1 Hz, 2H); (CD$_2$CN) $\delta$ 1.23 (t, $J$ = 7.1 Hz, 3H), 4.08 (q, $J$ = 7.1 Hz, 2H). *Ref 15: $^1$H NMR (CDCl$_3$) $\delta$ 1.46 (t, $J$ = 7.1 Hz, 3H), 3.15 (s, 3H), 4.55 (q, $J$ = 7.1 Hz, 2H). *Ref 34: $^1$H NMR (CD$_2$CN) $\delta$ 1.42 (t), 4.44 (q), 4.80 (m). *Benzy1 bromide. Aromatic part not shown. *Ref 15: $^1$H NMR (CDCl$_3$) $\delta$ 1.43 (t, $J$ = 7.2 Hz, 3H), 4.54 (q, $J$ = 7.2 Hz, 2H), 7.22 (s, 5H). *Ref 34: $^1$H NMR (CDCl$_3$) $\delta$ 1.30 (t), 4.55 (q), 4.93 (s). *Assignment is uncertain. *Ref 66: $^1$H NMR (CDCl$_3$) $\delta$ 1.25 (t, 3H), 4.15 (q, 2H), 5.1 (s, 2H), 7.35 (s, 5H).*

**Table 2.** Ratio of Alkylation Products of Ethyl N-Nitrosocarbamate Anion

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<tr>
<th>R</th>
<th>solvent</th>
<th>T ($^\circ$C)</th>
<th>53 ratio</th>
<th>43 ratio</th>
<th>total yield (%)</th>
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<tr>
<td>Me</td>
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<td>0.2</td>
<td>0.03</td>
<td>95</td>
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<td>CD$_2$Cl$_2$</td>
<td>20</td>
<td>1.4</td>
<td>0.2</td>
<td>85</td>
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<td>65</td>
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<td>7.1</td>
<td>0.0</td>
<td>60</td>
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<tr>
<td>PhCH$_2$</td>
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<td>6.7</td>
<td>b</td>
<td>40</td>
<td>7.1</td>
<td>0.0</td>
<td>60</td>
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*Established by integration of $^1$H NMR signals. See text for details.

*Solvent peak interference.

**Scheme 5**

The thermal stability of O-isomers 5b and 5d was assessed using mixtures of alkylated regioisomers isolated from the reactions of 2-Bu$_4$N in CH$_2$Cl$_2$ by flash chromatography. During the isolation process the ratio of O/N products decreased, indicating that about 15% of the O-isomer decomposed upon contact with silica gel and handling at ambient temperature. The salt-free solutions of the regioisomers in CD$_2$Cl$_2$ were monitored at 35 $^\circ$C by $^1$H NMR. As the reaction proceeded, the signals characteristic for O-isomers 5 disappeared simultaneously with the appearance of only one new set of signals assigned to alkyl ethyl carbonate 10 (Figure 1 and Scheme 6).

Monitoring of the ratio of the O-alkyl derivative to the N-alkyl regioisomer showed that the decomposition of 5 in CD$_2$Cl$_2$ is a first-order process with rate constants $k = 1.77 \pm 0.02 \times 10^{-5}$ s$^{-1}$ for 5b and $k = 4.78 \pm 0.08 \times 10^{-5}$ s$^{-1}$ for 5d. This compares to $k = 18.5 \pm 0.1 \times 10^{-5}$ s$^{-1}$ for the decomposition of anion 2-Bu$_4$N under identical conditions. The same measurements performed for 5d in CD$_2$CN gave $k = 3.20 \pm 0.01 \times 10^{-5}$ s$^{-1}$. The formation of carbonate 10 is concomitant with the disappearance of the O-alkyl derivative 5, and the process is also first-order. The absolute values of the rate constants for the two processes measured for 5d in CD$_2$Cl$_2$ are approximately equal.

**Quantum-Mechanical Calculations.** To provide a better understanding of the chemical processes and transformations involving 2-5, a series of calculations at the MP2(fc)/6-31+G(d)//MP2(fc)/6-31G(d) level were performed. Thus, conforma-


Conformational analysis for N-carboxyldiazotate anion (11) and three methylation products 12–14 established the structures and energies for their global conformational minima. Transition structures for cis–trans isomerization of 11–14 were calculated. Subsequently, the transition structures, and the pre- and post-transition complexes for gas-phase alkylation reactions of 11 with CH₃Cl were located. Finally, unimolecular thermal decomposition reactions of anion 11 and the methyl derivatives 12–14 were investigated.

Conformational Analysis and Ground State Structures. Calculations show that the planar (Cₛ) trans-diazotate anion 11a-E (Figure 2) with the s-cis configuration of the C–N bond represents the global minimum on the potential energy surface (PES). The planar s-trans conformer 11b-E represents a local minimum on the PES and is less thermodynamically stable than the planar s-cis isomer 11a-E by ΔGₒ = 0.4 kcal/mol (Figure 2). The two conformers interconvert through a transition structure 11a/b-E(TS) and a barrier ΔGₒ = 5.4 kcal/mol.

Two conformers of the cis-diazotate anion, 11a-Z and 11b-Z, are nonplanar in their equilibrium geometries and are thermodynamically less stable than 11a-E by ΔGₒ = 5.9 and 4.9 kcal/mol, respectively (Figure 2). While the O=C–N–N bond angle in the pseudo-s-cis conformer 11a-Z is θ = 41.2°, the analogous pseudo-s-trans structure could not be located on the PES. Instead, structure 11b-Z with a pseudo-orthogonal orientation of the COOH group with respect to the N–N–O plane (θ = 103.9°) was found. The syn orientation of the two groups in 11b-Z results in close contact between the carboxyl group and the oxygen atom (d_C=O = 2.461 Å), which presumably provides additional stabilization. Conformer 11b-Z converts to 11a-Z through transition state 11a/b-Z(TS) with a barrier ΔGₒ = 1.7 kcal/mol.

Conformational analysis of the N-methylation product found four planar ground state structures, among which 12a represents the global minimum on the PES. The calculated 1,2-anti-2,3-anti configuration of 12a is consistent with the results of previous calculations for the methyl ester of 12 and the reported solid state structure of N,N′-dimethylnitrosourea. The rotation of the carboxyl group around the C–N bond leads to 12b with a 1,2-syn-2,3-anti configuration, which is less thermodynamically stable than 12a by ΔGₒ = 1.6 kcal/mol. A much larger decrease in thermodynamic stability is observed for conformers with a syn orientation between the carboxyl and the nitroso groups. For instance, 12c with a 1,2-anti-2,3-syn configuration is less stable than 12a by ΔGₒ = 5.6 kcal/mol. This is consistent with literature results for the methyl ester of 12. A nonplanar structure with the s-cis configuration of the N–N bond could not be located on the PES, and the resulting equilibrium molecular geometry was that of 12c. The interconversion of the methyl ester of 12a to its methyl analogue of 12c requires ΔE₀ = 17.4 kcal/mol of activation energy.

Optimized geometries for conformers 12a–d are shown in Figure 2, and the structures and data for all conformers are listed in the Supporting Information.

A conformational search for azoxy derivative 13 located only one trans isomer 13-E and one cis isomer 13-Z on the PES (Figure 2). The latter was found to be more thermodynamically stable than the trans isomer by ΔGₒ = 6.3 kcal/mol. The trans isomer 13-E adopts a s-cis configuration around the C–N bond. In contrast, the carboxyl group in the cis isomer 13-Z is almost

development of double bond character for the N–N anion frequency in the normal modes shows that the isomerization in Wiberg bond order index (WBOI) decreases in the transition states. Thus, for anion of bond order and charge distribution between the ground and atom. These mechanistic pathways are consistent with changes in the transition structures.

The activation energies listed in Figure 3 show that anion 11 for isomerization about the N–N and diazene 14–E, respectively (Figure 3). In the formation of azoxy 13, are in equilibrium in solution in a ratio of about 2:1, and both can undergo alkylation reactions. In contrast, the concentration of the cis isomer 11 is expected to be 4 orders of magnitude lower than the trans isomer and not compete for the electrophile.

According to calculations, the two trans conformers, 11a-E and 11b-E, are in equilibrium in solution in a ratio of about 2:1, and both can undergo alkylation reactions. In contrast, the concentration of the cis isomer 11-Z is expected to be 4 orders of magnitude lower than the trans isomer and not compete for the electrophile.

Investigations of gas-phase alkylation reactions of anion 11-E with methyl chloride located transition structures 11TS12, 11TS13, and 11TS14 as well as the corresponding pre- and post-transition complexes for the formation of three regioisomers 12–14, respectively (Figure 6). In the formation of azoxy 13, the Cl(−) anion deprotonates the carboxyl group and the post-transition complex is not shown.

### Table 3. WBOI for Selected Compounds

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<td>1.24</td>
<td>1.33</td>
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<td>11-E/Z(TS)</td>
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<td>13-Z</td>
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<td>13-Z/E(TS)</td>
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<td>14-E/Z(TS)</td>
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<td>1.10</td>
<td>1.96</td>
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</table>

In all three reactions the electrophile approaches the nucleophile in the π plane, and consequently all complexes and transition structures are planar or close to planarity, as indicated by θ₁ and θ₂ in Figure 6. This suggests that the electrophile interacts with the anion lone pairs that constitute the anion’s HOMO (Figure 5). The lowest activation energy of ΔG°₂⁹⁸ = 19.5 kcal/mol was calculated for the N-alkylation and the highest activation energy was found for the formation of the azoxy derivative 13 (ΔG°₂⁹⁸ = 23.3 kcal/mol).

The formation of 13 and 14 begins with the s-cis conformer 11a-E. In contrast, the formation of 12 proceeds through transition structure 11TS12 derived from the less thermodynamically stable s-trans form of the anion, 11b-E. The product derived from 11a-E would lead to a conformational transition structure, while methylation of 11b-E gives 12a, which represents the global conformational minimum for 12. This preference for the orientation of the COOH group is presumably dictated by the generally more favorable steric interaction between the methyl group and the carbonyl, C–H···O=C, rather than analogous interactions with the OH group, C–H···O=C in the transition state.

The N(1) and O-alkylation reactions lead directly to the most thermodynamically stable isomers 12a and 14-E, respectively. In contrast, N(2) methylation results in the less thermodynamically stable trans isomer 13-E, which is likely to convert to the thermodynamic product 13-Z through a relatively low isomerization barrier of ΔG°₂⁹⁸ = 16.3 kcal/mol. Results for all three alkylation processes are presented graphically in Figure 7, and full computational data is listed in the Supporting Information.

Decomposition Processes. The experimental data suggest that the decomposition of anion 2 and alkoxydiazene 5 and the formation of carbonates 9 and 10, respectively, are concerted and related processes. Both processes require direct interactions of the oxygen atom bound to the nitrogen atom with the carbonyl...
group carbon atom in a four-center transition state. A similar process has been proposed as a first step in the decomposition of 3 and can also be envisioned for the intramolecular rearrangement of the azoxy derivatives.

A transition state search located structures 11b-Z(TS) and 14-Z(TS), which are higher in energy than the corresponding local minima (11b-Z and 14-Z) by $\Delta G^\ddagger_{298} = 15.9$ and 20.7 kcal/mol, respectively (Figure 8). The gas-phase calculated activation energy for the decomposition of 11 is significantly lower than the experimental value of $\Delta G^\ddagger_{298} = 23.3$ kcal/mol measured for 2-BuN in solution (Table 4). Analysis of molecular structures confirmed the four-center cyclic transition states 11-Z(TS) and 14-Z(TS) in which the O–C–O distance is 1.482 and 1.964 Å, respectively.

The cis isomers required for the concerted decomposition reaction are accessible from the more thermodynamically stable trans isomers through a trans–cis isomerization process. Both overall decomposition processes are highly exothermic by about 90 kcal/mol with respect to precursors 11a-E and 14-E. A graphical representation of the entire decomposition process is shown in Figure 9.

An alternative nonconcerted decomposition of 14-E through the homolysis of the O–N bond and formation of a radical pair is calculated to be significantly endothermic ($\Delta H = 50.5$ or $\Delta G_{298} = 37.7$ kcal/mol) and almost certainly does not compete with the concerted mechanism under the reaction conditions. The overall $\Delta G_{298}$ for breaking the two bonds is only slightly negative by $-6.0$ kcal/mol. The feasibility of the nonconcerted heterolytic process is difficult to assess without an adequate solvation model, and it was not attempted here.

Elimination of N$_2$ from 3 and 4 in a concerted process is not possible because of the presence of an alkyl substituent on the nitrogen atoms. Therefore, their decomposition is necessarily a two-step process involving an intramolecular rearrangement through a four-center transition state, followed by a heterolytic cleavage of the N–O bond in the resulting intermediate ester as shown in Scheme 7 for the model analogues.

Indeed, calculations located four-centered transition states 12-Z(TS) and 13-Z(TS) that lead to azo ester 17 and ion pair 18 (Figure 8). The calculated activation energies for the rearrangement are significantly higher than those found for 11 and 14 and are $\Delta G^\ddagger_{298} = 29.7$ and 40.7 kcal/mol for 12-Z and 13-Z, respectively (Table 4). The activation energy for 12-Z compares very well to the experimental value of $\Delta G^\ddagger_{298} = 30.5 \pm 1.2$ kcal/mol measured for 3a in pseudocumene.


Table 4. Activation Energies for Decomposition and Rearrangement Reactions

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\Delta H^\ddagger$ (kcal/mol)</th>
<th>$\Delta S^\ddagger$ (cal/mol•K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>(calcld)$^a$ 15.2</td>
<td>-2.5</td>
</tr>
<tr>
<td>2-BuN</td>
<td>(exptl) 23.3</td>
<td>0.0</td>
</tr>
<tr>
<td>12</td>
<td>(calcld)$^a$ 29.3</td>
<td>-1.4</td>
</tr>
<tr>
<td>3a</td>
<td>(exptl)$^b$ 29.4</td>
<td>-3.8</td>
</tr>
<tr>
<td>13</td>
<td>(calcld)$^a$ 39.6</td>
<td>-3.8</td>
</tr>
<tr>
<td>14</td>
<td>(calcld)$^a$ 25.2</td>
<td>-0.4</td>
</tr>
</tbody>
</table>

$^a$ MP2(fc)/6-31+G(d)/MP2(fc)/6-31G(d) calculations. $^b$ Ref. 43.
Ambident Ethyl N-Nitrosocarbamate Anion

Ambident Ethyl N-Nitrosocarbamate Anion

Experimental results show that the methylation of the ambident ethoxycarbonyldiazotate anion 2 occurs preferentially at the N(1) site leading to nitrosourethane 3a, while the other two isomers 4a and 5a are formed in significantly smaller quantities. The observed distribution of products is practically solvent-independent and correlates well with the theoretical activation energies $E_a$. Figure 10 shows a plot of the difference in enthalpy of activation versus the In of the ratio of isomers both relative to 3a (Table 2). The best fit line has a slope of 1.27, which is smaller than the ideal value of 1.84 for a reaction carried out at 0 °C. This suggests that the actual activation energies for the reaction of 2 with MeI in solution are smaller by a factor of 1.45 than those calculated for 11 and MeCl in the gas phase. Besides the systematic computational error, the difference in activation energies presumably reflects two competing effects related to the reaction medium and the nature of the electrophile. Typically, a change of reaction medium from gas phase to dipolar aprotic solvent increases $E_a$ by $0.45 \text{ kcal/mol}$, while substituting MeI for MeCl decreases $E_a$ by $0.45 \text{ kcal/mol}$. Both effects are of similar magnitudes and, based on the available data, 44,45 the electrophile effect is dominant. This is consistent with the slope of the line in Figure 10.

Increasing steric demand of the electrophile results in an increase of the diazene/nitroso ratio (5/3) from about 0.2 for methyl to about 7 for isopropyl. Again, the ratio of products is virtually solvent-independent, suggesting that the anion is practically free in both solvents. Unfortunately, the increase of relative yield of 5 is concomitant with a decrease of the overall yield of the reaction because of the competitive thermal decomposition of anion 2. The azoxy/nitroso ratio (4/3) also increases for ethyl, but in the reaction with isopropyl iodide 4c was not detected. Similar results were observed for alkylation of arenediazotate anions in DMSO or DMF, but no azoxy compound has been isolated or reported.17

The observed regioselectivity in alkylation of 2 and arene analogues is in sharp contrast with the results of alkylation of alkandiazotates in HMPTA, which show azoxy and O-alkyl derivatives as the major products.14 This difference in distribution of the regiosomers is most likely related to the distribution of electron density in the ambident anions. Since the alkyl group does not stabilize the negative charge on N(1), the electron density is shifted from N(1) toward the oxygen atom enhancing nucleophilicity of N(2) and O in alkandiazotates in comparison with nitrosourethane anion 2. Thus, the positive charge on the N(2) atom decreases from +0.26 in 2 to +0.18 in MeN=NO−, and the negative charge on the oxygen increases by 0.18, according to NBO calculations. Steric shielding of the N(1) nitrogen atom by the alkyl group is likely to be another factor affecting the regioselectivity of the alkylation.

Theoretical analysis of the alkylation reaction of 2 reveals that the electrophile approaches the anion in the π plane. This closely resembles the computational results for alkylation of enolates in which the in-plane attack on the oxygen lone pair has a substantially lower activation energy when compared to C-attack, which is necessarily perpendicular to the π plane.29–31 The O-attack is less sterically demanding and does not require disruption of conjugation in the transition state. Unlike enolates, all three atoms (two N and one O) in diazotates have unshared electron pairs (Figure 5) that can participate in transition states which can participate in transition states without involving the π electrons. According to the results of NBO calculations for 11a-E, the Mulliken charges on the oxygen and nitrogen N(1) atoms are similar and significantly negative, while the central nitrogen atom N(2) has a net positive charge (Figure 4). Since under similar circumstances nitrosonium is known to be more nucleophilic than oxygen and the electron density of the two atoms in the diazotate anion is comparable, the N(1) center would effectively compete for the electrophile, as long as it is not too sterically shielded. In contrast, the second nitrogen atom N(2) is expected to be much less competitive for the electrophile largely because of low electron density. These qualitative arguments are in good agreement with the observed distribution of products and results of theoretical analysis for 2 and also for alkandiazotates (vide supra).

Calculations demonstrate that the concerted four-center mechanism for the decomposition of anion 2 and azene 5 is consistent with reaction products (carbonates 9 and 10, respectively) and that the transition states are energetically accessible under the experimental conditions. The mechanistically required cis isomers 2-Z, and 5-Z are presumably formed in situ by isomerization of the corresponding trans isomers.

The anion 2-E is in equilibrium with the less thermodynamically stable cis isomer 2-Z through a relatively low interconversion barrier (calcd $\Delta G^\ddagger_{298} = 13.7 \text{ kcal/mol}$; Figures 3 and 9). The cis isomer is present in small quantities and decomposes through a barrier of about $\Delta G^\ddagger_{298} = 23.3 \text{ kcal/mol}$ (calcd $\Delta G^\ddagger_{298} = 15.9 \text{ kcal/mol}$), which represents the rate-determining step.
The 7.4 kcal/mol difference between the theoretical and experimental activation energies can be ascribed to solvent interactions with the anion.\textsuperscript{47} Similar solvation effects can be expected for the trans–cis isomerization of 2. Consequently, the relative difference between activation energy for isomerization and decomposition is expected to remain approximately the same in the gas phase and in solution.

In contrast to the reaction pathway for anion 2, the trans–cis isomerization of diazene 5 is the rate-determining step and requires higher energy (calcd $\Delta G^2_{298} = 25.3$ kcal/mol) than that for the decomposition through a four-center transition state (calcd $\Delta G^2_{298} = 21.1$ kcal/mol). Since 5 is a neutral molecule, solvent effects are expected to have relatively small impact on the energy. This is evident from the close match between experimental and theoretical $\Delta G^2_{298}$ values for the decomposition of another neutral compound, 3a (Table 4).

The mechanistic analysis and computational results for 11 and 14 are consistent with experimental data for 2 and 5. The observed nearly 10-fold higher rate for the decomposition of anion 2 than of azene 5 is consistent with the calculated lower stability of the former. Moreover, in both cases the cis isomers, 2-Z and 5-Z, are predicted to be transient species present in concentrations below the detection limit. This is in agreement with the fact that only single isomers for 2 and 5, most likely 2-E and 5-E, are observed in the solution by NMR.

Rearrangement of nitrosourethane 3 and azoxy 4 through a similar concerted four-center mechanism requires significantly higher activation energies than those predicted for 2 and 5. The value of $\Delta G^2_{298} = 29.7$ kcal/mol calculated for 12 is within the error bar of the experimental value of $\Delta G^2_{298} = 30.5 \pm 1.2$ kcal/mol obtained for 3a,\textsuperscript{53} which further validates the computational results. Considering the experimental measured rate constant of $k = 0.016 \times 10^{-3}$ s$^{-1}$ for 3a at 70 °C,\textsuperscript{43} compounds 3 and 4 should be thermally stable under our experimental conditions including heating for 1 h at 80 °C in MeCN. Surprisingly, azoxy 4, with the highest calculated activation energy of $\Delta G^2_{298} = 40.7$ kcal/mol, disappeared from the NMR spectrum under these conditions. Since an authentic sample of 4b shows no trace of decomposition in CD$_3$CN at 80 °C for 1 h, the observation made for the crude reaction mixture can be explained by the presence of a base generated from the decomposition of the anion 2. Unlike the case of 2 and 5, the products of the decomposition of 3 and 4 are unstable and undergo further heterolysis producing alkyl/diazonium ions.

The cis–trans isomerization of the N=N bond plays an important role in the stability of the anion and the allylketene products. Generally, low isomerization barriers are expected for the allyl-type system, Y–N=N–X ⇔ Y–N=N–X*, in which X and Y reduce the bond order between the nitrogen atoms by sharing the lone pair of X and stabilizing the negative charge on the other nitrogen atom by Y. A very favorable combination of X and Y is found in nitrosourethane 2 in which the carbonyl group stabilizes the negative charge on the nitrogen atom. As a result, the essentially single N=N bond (see 11-E/Z(TS) in Figure 3 and Table 3) The energy for isomerization increases when the carbonyl group is replaced with an aromatic group\textsuperscript{16,22,52,53} and is completely inhibited in alkanediazotates.

\textbf{Figure 11.} Generalized mechanisms for decomposition of nitroso and diazo derivatives.

\begin{center}
\includegraphics[width=0.5\textwidth]{figure11.png}
\end{center}


\textsuperscript{(52) Le Fèvre, R. J. W.; Sousa, J. B. J. Chem. Soc. 1953, 3154–3159.}


\textsuperscript{(55) Our results are consistent with the 48.8 kcal/mol barrier to Z→E isomerization in the neutral methanediazohydroxide calculated as $\Delta \text{SCF}$ at the HF/6-31G* level of theory in ref 54.}


NO₂C₆H₄N−N=O−OMe⁵⁹ toward elimination of N₂ and the formation of Ar−OMe at low temperature can be explained by the participation of the ipso carbon atom in the transition state according to mechanism A in Figure 11.

The mechanism shown in Figure 11 represents a concerted alternative to a nonconcerted heterolytic or homolytic decomposition pathway for the considered compounds. It can be speculated that the choice between these mechanisms depends largely on (i) the ability of the molecule to adopt the cis configuration (relative thermodynamic stability of the conformers and cis- and trans-isomers⁴³,⁶⁰), (ii) the ability of groups Y and R to support the positive charge, and (iii) the medium (polarity, protic solvents, and pH⁶¹). For simple systems such as compounds 2–5 in nonpolar and nonprotic solvents the concerted pathway appears to be preferred.

Finally, the experimental and computational data allow us to comment on a report describing the isolation of methoxydiazene 5a from a reaction of 2-Ag and MeI and its purification by vacuum distillation at 84 °C.⁹ The preparation could not be repeated in our lab, and the thermal stability of 5a required for distillation is doubtful. On the basis of the decomposition constant measured for 5b (k = 1.77 × 10⁻⁵ s⁻¹) at 35 °C and the calculated activation energy for 14-Z (25.3 kcal/mol), the estimated half-lifetime for 5a at 84 °C is about 2 min.

Conclusions

Alkylation of an essentially free diazotate anion 2 in solution gives three regioisomers in yields that are affected by the nature of the electrophile. With more bulky electrophiles, the less likely products are formed because the steric hindrance of the substituent favors the trans orientation in the transition state. The observed low yield and 39.5 ppm for 13C relative to TMS. Elemental analysis was provided by Atlantic Microlab, Norcross, GA.

Reaction of 2-Bu₄N with Alkyl Halides. General Procedure. The Bu₄N salt of nitrosourethane anion 2-Bu₄N (25 mg, 0.07 mmol) was dissolved in NMR solvent (CDCl₃ or CD₃CN, 0.25 mL) and transferred into an NMR tube. A solution of the alkylation agent (0.07 mmol) in the same solvent (0.25 mL) was added at 0 °C (for MeI and PhCH₂Br) or ambient temperature (EtI and i-PrI), and the progress of the reaction was monitored by 1H NMR. Characteristic chemical shifts are listed in Table 1.

Thermolysis of the Anion 2 and Kinetic Measurements. The reaction mixtures obtained in CH₂Cl₂ were passed through a silica gel plug to remove the ammonium salts, and the regioisomers were quickly eluted with methylene chloride as one fraction. The solvent was carefully evaporated, and the resulting oily residue of products was dissolved in CDCl₃ (0.5 mL). The solution was kept at 35 °C, and 1H NMR spectra were collected at regular intervals until almost complete disappearance of the starting material resulted.

The ratio of intensities of the signals of the ethyl group quartet in 2 (4.16 ppm) and the butyl group pseudotriplet in Bu₄N⁺ (3.22 ppm) was used to calculate the rate constant. The major products of the decomposition of 2 were identified as monoethyl carbonate [δ = 1.12 (t, J = 7.1 Hz, 2H) and 3.79 (q, J = 7.1 Hz, 2H)] and ethanol [δ = 3.62 (q, J = 7.1 Hz, 2H)].

Thermal Stability of the O-Alkyl Derivatives. General Procedure for Kinetic Measurements. The reaction mixtures obtained in CH₂Cl₂ were passed through a silica gel plug to remove the ammonium salts, and the regioisomers were quickly eluted with methylene chloride as one fraction. The solvent was carefully evaporated, and the resulting oily residue of products was dissolved in CDCl₃ (0.5 mL). The solution was kept at 35 °C, and 1H NMR spectra were collected at regular intervals. The ratio of intensities of the signals of the O-alkyl methylene group in the starting material (5a: 4.56 ppm; 5d: 5.52 ppm) to that in the N-alkyl derivative (5b: 3.77 ppm; 5d: 4.91 ppm) was used to calculate the rate constant. The major products of the decomposition...
of 5b and 5d were identified as diethylcarbonate (10b) and benzyl ethylcarbonate (10d). For 1H NMR spectral information see Table 1.

**Ethyl $N$-Nitrosocarbamate Silver Salt (2-Ag).** $N$-Nitrourethane ammonium salt (6-NH$_4$) was dissolved in a mixture of water (30.0 mL) and acetic acid (1.6 mL). Zn dust (1.20 g, 18.35 mmol) was added portionwise at a rate to ensure that the temperature was under 25 °C during the addition (a small amount of ice can be added directly to the reaction mixture if the temperature rises above 30 °C). Stirring was continued for 1 h during which a significant amount of yellow precipitate was formed. Ice was added, followed by aqueous ammonia, in excess. The resultant suspension was stirred for 5 min, followed by a solution of AgNO$_3$ (2.25 g, 13.23 mmol). Acetic acid was added in small portions to make the solution acidic, causing the formation of a yellow precipitate. The mixture was left standing for 10–15 min, and the resulting solid was filtered and washed successively with water, ethanol, and methanol. The solid was dried in a vacuum at 0 °C to give 1.50 g (50% yield) of the silver salt 2-Ag as a yellow powder. Anal. Calcd for C$_3$H$_5$AgN$_2$O$_3$: C, 16.02; H, 2.24; N, 12.45. Found: C, 15.74; H, 2.13; N, 11.87.

**Ethyl $N$-Nitrosocarbamate Tetrabutylammonium Salt (2-Bu$_4$N).** The silver salt 2-Ag (1.50 g, 6.67 mmol) was suspended in an ice--water mixture, and a solution of Bu$_4$NBr (2.36 g, 7.34 mmol) was added to a stirred solution of ethyl 2-ethylcarbazate (85% pure, 1.50 g, 7.4 mmol) was slowly added in small portions to the stirred solution of ethyl 2-ethylcarbazate (7), 0.40 g, 3.0 mmol) in methylene chloride (25 mL) at 0 °C. After 4 h the heterogeneous reaction mixture was allowed to warm to ambient temperature, and stirring was continued overnight. After a total of 12 h, the initially developed yellow color of the transient azo compound largely disappeared. The suspension of the acid was filtered off, and pale yellow filtrate was washed with NaHCO$_3$ and dried (Na$_2$SO$_4$). The solution was passed through a silica gel plug giving 0.35 g of essentially pure product by TLC. An analytical sample was obtained by column chromatography (CH$_2$Cl$_2$/hexanes in 2:1 ratio) as a yellowish oil: 1H NMR (CD$_2$Cl$_2$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.29–1.41 (m, 8H), 1.52–1.63 (m, 8H), 3.17–3.23 (m, 8H), 4.14 (q, J = 7.1 Hz, 2H); (CD$_3$CN) δ 0.93 (t, J = 7.2 Hz, 12H), 1.23 (t, J = 7.1 Hz, 3H), 1.25–1.35 (m, 8H), 1.52–1.58 (m, 8H), 3.05–3.10 (m, 8H), 4.08 (q, J = 7.1 Hz, 2H); δ(C) 13.7, 15.0, 20.0, 24.3, 59.0, 60.0, 168.0. Anal. Calcd for C$_6$H$_{11}$N$_2$O$_2$: C, 63.47; H, 11.49; N, 11.69. Found: C, 62.89; H, 11.72; N, 9.74.

**Ethyl $N$-Nitrosocarbamate Ammonium Salt (6-NH$_4$).** It was prepared in 85% yield according to a literature procedure by nitration of urethane in a KNO$_3$/H$_2$SO$_4$ mixture: mp 165–166 °C dec (lit. 164–165 °C); 1H NMR (DMSO-d$_6$) δ 1.10 (t, J = 7.1 Hz, 3H), 3.87 (q, J = 7.1 Hz, 2H); 13C NMR (DMSO-d$_6$) δ 59.3, 160.5.

**Ethyl 2-Ethylcarbazate (7).** A solution of ethyl carbazate (6.14 g, 59.0 mmol) and acetaldehyde (2.60 g, 59 mmol) in ethanol (50 mL) was stirred at ambient temperature until all aldehyde reacted (about 2 h). Ethanol was evaporated, the semicrystalline white residue was treated with ether, and the ether was evaporated leaving a white solid mixture of carbazole isomers 8: 1H NMR (CD$_2$Cl$_2$) δ isomer A: 1.26 (t, J = 7.2 Hz, 3H), 1.79 (d, J = 5.5 Hz, 3H), 4.15 (q, J = 7.2 Hz, 2H), 6.74 (pseudo d, J = 5.0 Hz, 1H), 8.05 (br s, 1H); isomer B: 1.26 (t, J = 7.2 Hz, 3H), 1.92 (d, J = 5.4 Hz, 3H), 4.18 (q, J = 7.2 Hz, 2H), 7.22 (pseudo d, J = 4.7 Hz, 1H), 8.27 (br s, 1H).

A solution of borane in THF (1.0 M, 62 mL, 26 mmol) was slowly added to the crude solid carbazole at 0 °C. The resulting clear colorless solution was stirred for 20 min and quenched by addition of 10% HCl (30 mL). The biphasic mixture was stirred at 50 °C for 2 h and, when all hydride decomposed, neutralized with solid NaHCO$_3$. Organic products were extracted with ether (3 x), dried (Na$_2$SO$_4$), and solvent- evaporated. The thick oily residue was dissolved in methylene chloride (20 mL), passed through a silica gel plug (5 cm), and washed with methylene chloride (200 mL). The clear filtrate was evaporated leaving 6.3 g of crude ethyl 2-ethylcarbazate, which was purified by short-path distillation at 80 °C/0.7 mmHg: 1H NMR (CD$_2$Cl$_2$) δ 0.40 (t, J = 7.2 Hz, 3H), 1.23 (d, J = 7.1 Hz, 3H), 2.85 (q, J = 7.2 Hz, 2H), 3.4 (brs, 1H), 4.11 (q, J = 7.1 Hz, 2H), 6.2 (br s, 1H); δ(C) 13.16, 14.96, 46.76, 61.47, 157.95. The compound was obtained without further purification.

**Ethyl 1-Ethylazoxy-2-carboxylate (4b).** Solid m-chloroperbenzoic acid (85% pure, 1.50 g, 7.4 mmol) was slowly added in small portions to a stirred solution of ethyl 2-ethylcarbazate (7, 0.40 g, 3.0 mmol) in methylene chloride (25 mL) at 0 °C. After 4 h the heterogeneous reaction mixture was allowed to warm to ambient temperature, and stirring was continued overnight. After a total of 12 h, the initially developed yellow color of the transient azo compound largely disappeared. The suspension of the acid was filtered off, and pale yellow filtrate was washed with NaHCO$_3$ and dried (Na$_2$SO$_4$). The solution was passed through a silica gel plug giving 0.35 g of essentially pure product by TLC. An analytical sample was obtained by column chromatography (CH$_2$Cl$_2$/hexanes in 2:1 ratio) as a yellow oil: 1H NMR (CD$_2$Cl$_2$) δ 1.33 (t, J = 7.1 Hz, 3H), 1.54 (t, J = 7.4 Hz, 3H), 4.29 (q, J = 7.4 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H); (CD$_2$CN) δ 1.29 (t, J = 7.1 Hz, 3H), 1.48 (t, J = 7.3 Hz, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.31 (q, J = 7.3 Hz, 2H); δ(C) NMR (CD$_2$Cl$_2$) δ 13.11, 14.33, 64.45, 66.13, 158.20. IR: 1753, 1519, 1221 cm$^{-1}$. Anal. Calcd for C$_{19}$H$_{41}$N$_3$O$_3$: C, 63.47; H, 11.49; N, 9.74.

**Acknowledgment.** We are indebted to Ms. Krystyna K. Kulikiewicz, a visiting graduate student from University of Lodz, Poland, for help with isolation of the azoxy compound 4b. This project was supported by DARPA/AFOSR F49620-98-1-0483.

**Supporting Information Available:** Tables of kinetic data, computational results, and 1H NMR spectrum of 2-Bu$_4$N. This material is available free of charge via the Internet at http://pubs.acs.org.

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