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Concerted Bimolecular Substitution Reactions of Anilino Thioethers

Sherif Eldin and William P. Jencks*

Contribution No. 1785 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254-9110

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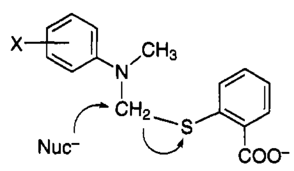
Abstract: The anilino thioethers, $3\text{-}NO_2\text{-}C_6H_4N(CH_3)CH_2SC_6H_4\text{-}2\text{-}COO^-$ (**1**) and $4\text{-}NO_2\text{-}C_6H_4N(CH_3)CH_2SC_6H_4\text{-}2\text{-}COO^-$ (**2**) undergo concerted bimolecular nucleophilic substitution (A_ND_N) with nucleophilic reagents in aqueous solution at 25 °C that is enforced by the absence of a significant lifetime for the corresponding iminium ion$\cdot^-$SAr intermediates. Electron donation from the aniline nitrogen atom provides assistance to the nucleophilic reaction and results in a dissociative character for the transition state of the reaction. A Swain−Scott correlation with $s \approx 0.4$ indicates an early transition state for bond formation, with a low sensitivity of the nucleophilic reaction toward the attacking nucleophile.

Introduction

We have been interested in how chemical reactions choose their mechanisms.[1] Classification of reaction mechanisms based on structure−reactivity correlations is problematic. There are concerted bimolecular substitution reactions (A_ND_N) with transition states that closely resemble those expected for a unimolecular S_N1 substitution mechanism ($D_N + A_N$).[2] In addition, a transformation from one mechanism to another may be accompanied by a gradual change in the character of the rate-determining transition state that provides no sharp boundaries between the two mechanisms. Therefore, it can be difficult or impossible to identify the point at which mechanisms change simply from analysis of the structure−reactivity parameters.

Reaction mechanisms are dictated by the lifetimes, or the lack thereof, of reaction intermediates that may be formed in the reaction, and knowledge of the lifetime of an intermediate permits a clear distinction between mechanisms.[1−3] A stepwise mechanism, in which an intermediate chemical species is formed, is followed when the intermediate has a lifetime that is longer than the time for a bond vibration, $\approx 10^{-13}$ s. This provides a sharp borderline between a stepwise and a concerted reaction mechanism that does not rely on structure−reactivity parameters. Studies[2−10] of carbocations and oxocarbenium ion intermediates with different stabilities support the above proposal and are consistent with the hypothesis or notion[2] *"that for substitution at carbon a stepwise mechanism will be followed when the intermediate exists and the stepwise mechanism is possible; the concerted mechanism is followed only when it is enforced by the nonexistence of the intermediate".*

We described earlier the solvolysis of anilino thioethers in aqueous solution in the absence of strong nucleophiles.[11] The solvolytic reaction proceeds through a stepwise mechanism in which a short-lived iminium ion intermediate is formed and reacts rapidly with water. We describe here a study of the reactions of the anilino thioethers **1** and **2** with a series of nucleophilic reagents by concerted bimolecular nucleophilic substitution. This mechanism is enforced by the absence of a significant lifetime for an iminium ion that is in contact with a thiolate ion or other nucleophilic reagents.



1: $X = 3\text{-}NO_2$
2: $X = 4\text{-}NO_2$

Experimental Section

Materials. Reagent grade inorganic salts and DMSO (Gold Label grade) were obtained from Aldrich Chemical Co., 2-mercaptoethanol (>99%) and ethylenediaminetetraacetic acid disodium salt from Fluka, and 4-mercaptobenzoic acid from Toronto Research Chemicals. Procedures for the synthesis and solvolysis of the anilino thioethers, *N*-methyl-*N*-[(2-carboxyphenylthio)methyl]-3-nitroaniline (**1**) and *N*-methyl-*N*-[(2-carboxyphenylthio)methyl]-4-nitroaniline (**2**), were described previously.[11]

All solutions were prepared with deionized distilled water and contained 1 mM EDTA. The pH values were measured with a 476541 Corning combination electrode attached to an Orion Model 701A pH meter. Spectrophotometric measurements were followed with a Cary 1E or a Perkin Elmer λ6 spectrophotometer.

Kinetics. A 50-μL aliquot from a stock solution of 0.02 M **1** or 0.002 M **2** in DMSO was added to a cuvette containing 3 mL of carbonate buffer of pH 10.0−10.5, 1 mM EDTA, and 0−1 M of a nucleophilic reagent at 25 °C and ionic strength 1.0, maintained with NaCl. The reaction was followed spectrophotometrically at 380 nm for **1** and 412 nm for **2**. The substitution products are generally unstable adducts that break down rapidly to the corresponding aniline and formaldehyde. However, the 2-mercaptoethanol adduct is more stable than the starting anilino thioether and undergoes solvolysis with a much slower rate. Individual runs followed first-order kinetics accurately for at least 4 half-times. The second-order rate constants for the nucleophilic reaction, k_N, were obtained from the slopes of plots of the

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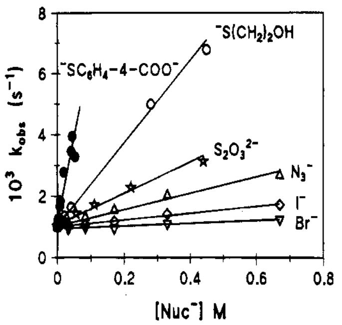

Figure 1. The dependence of the pseudo-first-order rate constants, k_{obs}, for the nucleophilic reaction with 3-nitroanilino thioether **1** on the concentration of nucleophiles in aqueous solution at 25 °C and a constant ionic strength of 1.0 (NaCl).

observed pseudo-first-order rate constants, k_{obs}, against nucleophile concentration.

Results

The anilino thioethers, X-$C_6H_4N(CH_3)CH_2SC_6H_4$-2-COO^- (X = 3-NO_2 and 4-NO_2), undergo solvolysis at 25 °C in aqueous solution containing 3% DMSO, 0.5 M carbonate buffer, and 1 mM EDTA at pH 10.0–10.5 and μ = 1 (NaCl). The solvolysis reaction was followed by monitoring (1) the formation of released thiolate with Ellman's reagent (DTNB) at 412 nm, (2) the release of thiolate anion directly in the range 250–270 nm, or (3) the change of absorbance in the visible range when the nitroanilino thioethers are cleaved to give the corresponding *N*-methylnitroanilines (at 380 and 412 nm for X = 3-NO_2 and 4-NO_2, respectively).[11] Rate constants for a given compound that were obtained by the above methods were in excellent agreement. There was no significant change in the rate constant for solvolysis with 0.02, 0.05, and 0.50 M carbonate buffer, pH 10.5, ionic strength 1.0 (NaCl). The reaction of 3-nitroanilino thioether **1** and 4-nitroanilino thioether **2** with nucleophilic reagents was monitored under the above conditions at 380 and 412 nm, respectively. The observed pseudo-first-order rate constants increase linearly with increasing nucleophile concentration (Figure 1).

Discussion

The Mechanism of the Displacement Reaction. The linear dependence of the observed pseudo-first-order rate constants for product formation on the concentration of the nucleophilic reagent, which is present in large excess, is indicative of the bimolecular nature of the displacement reaction. A possible mechanism for the substitution reaction involves decomposition of the anilino thioether to give the corresponding iminium ion, followed by the reaction of the iminium ion with the nucleophile as shown in the outer pathway in Figure 2. This is a $D_N + A_N$ (S_N1)[12] mechanism. However, the anilino thioethers, 3-NO_2-$C_6H_4N(CH_3)CH_2SC_6H_4$-2-COO^- (**1**) and 4-NO_2-$C_6H_4N(CH_3)CH_2$-SC_6H_4-2-COO^- (**2**), undergo solvolysis with first-order rate constants of 8.3×10^{-4} and 1.6×10^{-5} s^{-1}, respectively, in aqueous solution under the conditions used for the substitution reaction.[11] These rate constants for formation of the iminium ions are much smaller than the pseudo-first-order rate constants for the reaction of the iminium ions with nucleophiles. Therefore, if the substitution reaction were to proceed through the formation of a free, solvent-equilibrated iminium ion, followed by the reaction of the iminium ion with a nucleophile, we would not observe a change in the rate of the reaction with increasing nucleophile concentration. The observed increase in the reaction rate with increasing nucleophile concentration is inconsistent with a $D_N + A_N$ mechanism for the substitution reaction.

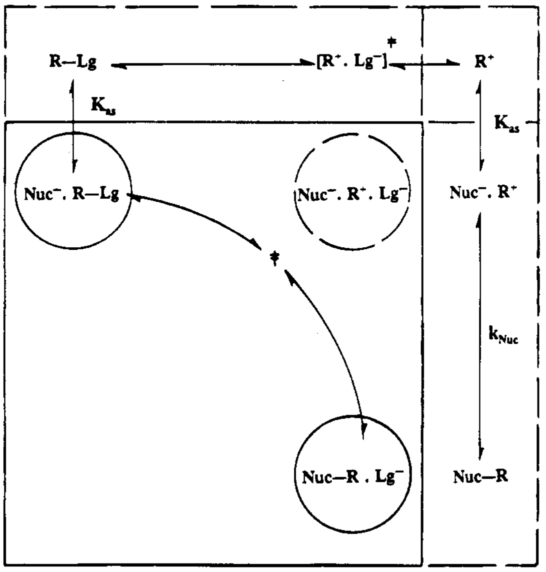

Figure 2. A reaction coordinate diagram for nucleophilic substitution on carbon. A stepwise reaction through a solvent-equilibrated carbocation intermediate follows the outer pathway. A concerted reaction follows the inner pathway and avoids the $Nuc^-{\cdot}R^+{\cdot}Lg^-$ complex because this species does not have a significant barrier for collapse to reactants or products.

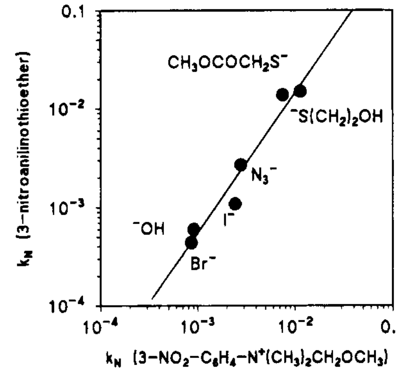

Figure 3. Comparison of nucleophilic reactivities toward 3-nitroanilino thioether **1** and *N*-(methoxymethyl)-*N*,*N*-dimethyl-*m*-nitroanilinium ion[4] in aqueous solution at 25 °C and a constant ionic strength of 1.0. The line has a slope of 1.4 and k_N is the second-order rate constant for the nucleophilic reaction.

A second possible mechanism for the substitution reaction is a preassociation stepwise mechanism ($A_N{*}D_N$). However, this requires the formation of a ternary nucleophile·iminium ion·leaving group intermediate. It has been established that in aqueous solution in the absence of strong nucleophiles, the anilino thioethers **1** and **2** undergo solvolysis forming the corresponding free solvent-equilibrated iminium ions $H_2C{=}N^+$-$(CH_3)C_6H_4$-X, with lifetimes in aqueous solution of 3.3×10^{-8} and 1.0×10^{-8} s for X = 3-NO_2 and 4-NO_2, respectively (k_{H_2O} = 3.0×10^7 and 1.0×10^8 s^{-1} for X = 3-NO_2 and 4-NO_2, respectively).[11] Since the nucleophilicity of a thiophenolate anion is about eight orders of magnitude larger than that of water,[13] the pseudo-first-order rate constant for the collapse of the iminium ion·$^-$SAr intermediates would be $\approx 10^{15.16}$ s^{-1}.[11] These rate constants are too large to represent a significant barrier for the collapse of the encounter complex, $ArS^-{\cdot}H_2C{=}N^+$-

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Table 1. Second-Order Rate Constants for the Reaction of Nitroanilino Thioethers with Nucleophiles in Aqueous Solution[a]

nucleophile	k_N (M^{-1} s^{-1}) 1	2
$^-SC_6H_4$-4-COO^-	9.7×10^{-2}	1.5×10^{-3}
$S_2O_3^{2-}$	5.1×10^{-3}	9.5×10^{-5}
N_3^-	2.7×10^{-3}	8.2×10^{-5}
I^-	1.1×10^{-3}	1.9×10^{-5}
^-OH	6×10^{-4}	
Br^-	4.4×10^{-4}	7.0×10^{-6}
H_2NNH_2	4×10^{-4}	9×10^{-6}
$^-SCH_2COCH_3$	1.5×10^{-2}	
$^-SCH_2CH_2OH$	1.4×10^{-2}	
H_2O	2.0×10^{-5}	2.5×10^{-7}

[a] Determined in 0.5 M carbonate buffer (except for the reactions with 2-mercaptoethanol or methylthioglycolate, in which the thiols were used for buffering), at pH 10–10.5, 25 °C, and $\mu = 1.0$ (NaCl).

$(CH_3)C_6H_4$-X. Therefore, the ion pair has no lifetime and the reaction must proceed through a preassociation concerted bimolecular substitution mechanism (A_ND_N). The absence of a significant lifetime for the encounter complex, $ArS^-{\cdot}H_2C{=}N^+$-$(CH_3)C_6H_4$-X, requires that in the solvolysis reaction the transition state for the formation of the solvent-separated iminium ion represents both bond-breaking and diffusional separation, as shown at the top of Figure 2.[11,14]

Concurrent $D_N + A_N$ and A_ND_N Mechanisms. It has been shown by Richard and Jencks[2] that concurrent $D_N + A_N$ and A_ND_N mechanisms can take place when a cationic intermediate has a significant lifetime in the solvent, but no lifetime when it is in contact with an added nucleophilic reagent. Therefore, it is possible that a fraction of the substitution reaction proceeds through a $D_N + A_N$ mechanism, in which the iminium ion intermediate reacts with ArS^-. However, this reaction pathway is limited by the slow solvolysis step (the Y-intercept of Figure 1), and is not significant in the presence of the faster A_ND_N reaction, as indicated in Figure 1.

Assistance from the Nitrogen Atom and the Structure of the Transition State. The results indicate that the lone-pair electrons on the aniline nitrogen atom provide assistance to the nucleophilic reaction. A *p*-nitro substituent on the aniline ring would inhibit electron donation from the aniline nitrogen atom more than a *m*-nitro substituent (the pK_a values for *N,N*-dimethyl-*p*-nitroaniline and *N,N*-dimethyl-*m*-nitroaniline in water are 0.61 and 2.63, respectively),[15] and this is reflected in the rate constants for the bimolecular nucleophilic substitution of anilino thioethers (Table 1). The second-order rate constants, k_N, for nucleophilic reactions with 4-nitroanilino thioether **2** are about 60-fold (2.5 kcal/mol) smaller than those for 3-nitroanilino thioether **1**. However, Figure 4 shows that the two anilino thioethers have the same relative sensitivities toward nucleophiles, as indicated by the slope of 1.0 for a correlation of log k_N for **1** *vs* that for **2**. This indicates that the location of the transition state on the energy surface for the nucleophilic reaction does not change significantly with changes of the substituent on the aniline ring; i.e. there is a sharp curvature of the energy surface for the nucleophilic reaction so that there is little or no change in the position of the transition state with a change in $\Delta G°$ for the reaction.[4,16]

The aniline nitrogen atom provides assistance for the reaction of nucleophiles with the methylene carbon atom by stabilizing a dissociative ("exploded") transition state, in which there is a relatively weak interaction between the nucleophile and the leaving group, as shown in **3**. Such transition states are

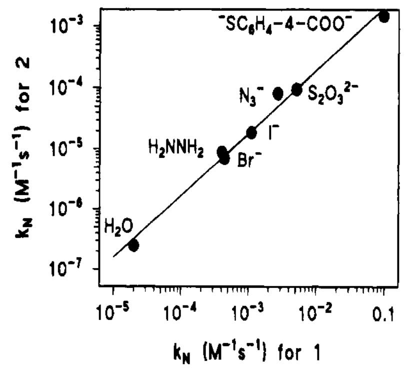
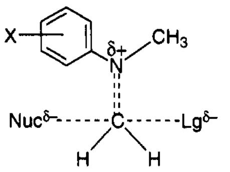


Figure 4. A correlation between log k_N for **1** and that for **2**, with a slope of 1.0.



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characterized by small slopes in Swain–Scott correlations.[4,8] We were unable to obtain a satisfactory Swain–Scott correlation for this system because of the low sensitivity toward nucleophiles and scatter in points. However, an estimate for the slope of the Swain–Scott correlation for the reaction of 3-nitroanilino thioether **1** with nucleophiles can be obtained by comparing this system with the reaction of nucleophilic reagents with *N*-(methoxymethyl)-*N,N*-dimethyl-*m*-nitroanilinium ion, a well-established reaction in which concerted bimolecular nucleophilic substitution proceeds through a highly dissociative transition state.[4] Figure 3 shows that the rate constants for the reaction of *N*-(methoxymethyl)-*N,N*-dimethyl-*m*-nitroanilinium ion with nucleophilic reagents correlate well with those for the reaction of **1** with the nucleophilic reagents, with a slope of 1.4. This indicates that the 3-nitroanilino thioether is 1.4-fold more sensitive toward nucleophilic reagents compared with *N*-(methoxymethyl)-*N,N*-dimethyl-*m*-nitroanilinium ion. The *s* value for the reaction of nucleophiles with *N*-(methoxymethyl)-*N,N*-dimethyl-*m*-nitroanilinium ion is 0.28;[4] therefore, we estimate that *s* for the reaction of **1** with nucleophiles is approximately $1.4 \times 0.28 \approx 0.4$. Thus, the reaction of **1** is 0.4-fold as sensitive to the structure of the nucleophile as the reference reaction of nucleophiles with methyl halides. This is consistent with the loose transition state **3** for nucleophilic substitution with anilino thioethers.

Conclusion. Reaction mechanisms that are enforced by the lifetime, or lack thereof, of reaction intermediates have been characterized previously with compounds that can generate carbocations and oxocarbenium ions.[3–10] This study demonstrates that reactions that can generate iminium ion intermediates follow the same behavior, in which the concerted mechanism is enforced by the absence of a barrier for collapse of an iminium ion-nucleophile ion pair. The solvolysis of nitroanilino thioethers in aqueous solution produces iminium ion intermediates with a significant lifetime. However in the presence of nucleophilic reagents, the reaction may proceed predominantly through bimolecular nucleophilic displacement (A_ND_N) of the nucleophile and the anilino thioether. A large number of chemical and enzyme-catalyzed reactions are known to proceed

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(14) There is precedent for such solvolytic reactions in which the intimate ion pair does not have a significant lifetime; i.e., the ion pair is rather a transition state that leads to the solvent-separated ions.[8]

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through unstable iminium ion intermediates. A physiologically important example is thymidylate synthase, which catalyzes the reaction of dUMP with N^5,N^{10}-methylene tetrahydrofolate to give dTMP. A stepwise mechanism involving an iminium ion intermediate has been proposed for this reaction.[17] However, the results reported here suggest that the enzyme-catalyzed reaction may proceed through concerted bimolecular substitution.

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