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Kinetics of the Reaction of *N,N*-Dimethylaniline with 1-Bromoalk-2-ynes

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Abstract—Quaternization of *N,N*-dimethylaniline with propargyl bromide, 1-bromobut-2-yne, and 1-bromooct-2-yne were studied. It was shown that, with the lengthening chain of the substituent at the triple bond, the quaternization rate tends to increase.

Keywords: nucleophilic substitution, quaternization of amines, reaction kinetics, carbocations

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The introduction of a propargyl group into molecules is the focus of a large number of articles and patents describing the synthesis, transformations, and biological properties of reaction products. At the same time, the mechanism (in particular, the kinetics and thermodynamics) of the nucleophilic substitution involving propargyl halides has been studied much less extensively than the allyl and benzyl analogs. For example, even for primary propargyl halides (the reactions with secondary derivatives are additionally complicated by isomerization) there exist fairly contradictory published data on the influence of the structure of the reaction participants on the reaction rate and mechanism [1, 2]. At present such reactions are primarily described based on calculations [3–5].

The electron-donor properties of alkyl groups (due to +*I* effect) typically (with exception of the Baker-Nathan effect) tend to increase as (H <) Me < Et < *i*-Pr < *t*-Bu. Therefore, in S_N1 reactions, the stability of the carbocation formed from $BrCH_2C{\equiv}CR$ and the reaction rate should exhibit the same trend. However, the rate of the alkaline hydrolysis of $RC{\equiv}CCMe_2Cl$ varies depending on the nature of R in a reverse order (see table). The rate of solvolysis in aqueous ethanol upon replacement of the hydrogen atom by the methyl group (as in the reaction of $RC{\equiv}CCH_2Cl$ with potassium iodide) initially increases and then begins to decrease (the solvolysis rate for Me_2RCCl under identical conditions tends to increase as dictated by the change in the +*I* effect [6]). The alkaline hydrolysis reactions of monosubstituted triple-bond propargyl halides (see the table, R = H) and their reactions with sodium ethoxide follow the S_N2 mechanism; otherwise the S_N1 mechanism operates.

Previously, we studied the kinetics of quaternization of saturated tertiary β-, γ-, and δ-alkynylamines with alkynyl bromides in acetophenone and calculated the activation parameters of those reactions [7]. We found that chain lengthening from 4 to 8 carbon atoms in the substituent at the triple bond in alkynyl bromides affects negligibly the rate of reaction (1) with tertiary β-, γ-, and δ-alkynylamines.

$$R^1_2NR^2 + BrCH_2C{\equiv}CR^3 \rightarrow [R^1_2NR^2CH_2C{\equiv}CR^3]^+\,Br^-, \quad (1)$$

$R^1 = CH_3, C_2H_5, C_4H_9, C_8H_{17}$; $R^2 = CH_2C{\equiv}CC_4H_9, (CH_2)_2C{\equiv}CC_4H_9, (CH_2)_3C{\equiv}CC_4H_9, C_8H_{17}$; $R^3 = C_4H_9, C_6H_{13}, C_8H_{17}$.

Kinetic studies showed that, in the reaction with propargyl bromides, β-alkynylamines are more nucleophilic than stronger bases (γ- and δ-alkynylamines) due to a greater accessibility of the reaction center, the nitrogen atom (with four C–C≡C–C atoms lying in one straight line). A special position of β-alkynylamines is confirmed by thermodynamic parameters. Low E_a and $\Delta H^{\neq}$ values indicate weak steric hindrance for these amines compared to γ- and δ-alkynylamines. More negative activation entropies for tertiary β-alkynylamines evidence a greater rigidity of the activated complex in reactions with these compounds.

Here we studied the kinetics of reaction (2) of quaternization of *N,N*-dimethylaniline **1** with propargyl bromide **2a**, 1-bromobut-2-yne **2b**, and 1-bromooct-2-yne **2c**, differing in the carbon chain length.

$$\underset{\mathbf{1}}{\mathrm{PhN(CH_3)_2}} + \underset{\mathbf{2a\text{–}2c}}{\mathrm{BrCH_2C{\equiv}CR^3}}$$

$$\rightarrow \underset{\mathbf{3a\text{–}3c}}{[\mathrm{PhN(CH_3)_2CH_2C{\equiv}CR^3}]^+\,\mathrm{Br}^-}, \tag{2}$$

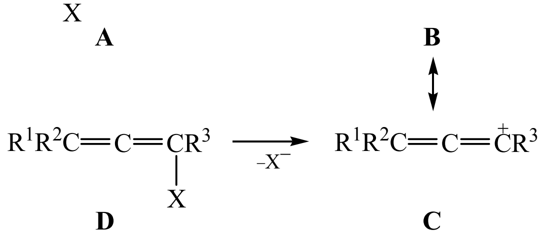
R^3 = H (**a**), CH_3 (**b**), *n*-C_5H_{11} (**c**).

Salts **3a–3c** are colorless crystalline substances that are readily soluble in water. Compound **3a** has been described in the literature [8]; the composition of salts **3b, 3c** was determined by elemental analysis for nitrogen and ionic bromine, and their structure was confirmed by ^{1}H NMR spectroscopy.

The rate of reaction (2) was followed by measuring the decrease in optical density of amine **1** with time at λ = 299 nm corresponding to the maximum of the longwave absorption band $n\rightarrow\pi^*$. Bromo derivatives **2a–2c** and salts **3a–3c** do not absorb in this spectral region.

Reaction (2) is accelerated on going from propargyl bromide to 1-bromooct-2-yne. The rate constants of the second-order reaction in acetonitrile at 30°C for halides **3a–3c** with lengthening R^3 substituent were estimated at 0.00636±0.00038, 0.0185±0.0011, and 0.0256±0.0011 L mol^{-1} min^{-1}, respectively.

Nucleophilic substitution reactions can follow the uni- (with the formation of carbocations) or bimolecular mechanisms, with one of them dominating [9]. Attempts to experimentally detect alkynyl carbenium ions were based on studying the kinetics of solvolytic processes [10]. To resonance forms of propargyl cations **B** belong allenyl ions **C**; these cations can be recovered by solvolysis of both acetylenic (**A**) and allenic (**D**) halides.



Kinetic data ($k\times10^4$, L mol^{-1} h^{-1}) for the alkaline hydrolysis and solvolysis of RC≡CCMe$_2$Cl at 25°C in 80% ethanol [1] and for the reactions of RC≡CCH$_2$Cl with potassium iodide at 20°C in acetone and with sodium ethoxide at 50°C in ethanol [2]

R	Alkaline hydrolysis	Solvolysis	Reaction with potassium iodide	Reaction with sodium ethoxide
H	7.1[a]	0.00237	0.279	–[b]
Me	4.9	5.13	0.419	2.24
Et	4.6	4.90	–	–
i-Pr	3.45	3.42	–	–
t-Bu	2.77	2.80	–	–

[a] Second-order reaction. [b] Reaction of complicated second-order.

The formation of alkynyl carbenium cations has been proven by various methods; the degree of delocalization and, consequently, the structure and behavior of such cations depend on the nature of the substituents and the reaction medium. The data on solvolysis for the series of halogen derivatives **A** and **D** under a wide variety of conditions show that the reactions follow the S_N1 mechanism, with halides **A** reacting much faster than the corresponding isomers **D** [10]. Factors favoring unimolecular process are enhanced stability of the carbocation resulting from halide dissociation and the use of protic solvents.

Reaction (2) seems to follow the bimolecular mechanism to a larger extent. First, the reaction rate constant calculated by the second-order reaction equation is invariant for all halides **2a–2c**. Second, the addition of quaternary salt **3a** to the reaction system in some of the experiments with propargyl bromide does not decelerate the reaction with amine **1** (*k* = 0.00652±0.00068 L mol^{-1} min^{-1}). The unimolecular reaction should be decelerated by the action of the same ion.

On the one hand, the differences in the chain length (volume) of substituents at the triple bond of compounds **2a–2c,** with their large separation from the reaction center, should not significantly affect the quaternization of amine **1.** On the other hand, the alkyl substituents differ in the magnitude of the inductive effect. The reaction is accelerated with increasing +*I* effect in bromides **2a–2c,** so the transition state stabilization is more significant than the decrease in the positive charge in the alkynyl bromide. The formation of a new bond in S_N2 reactions generally precedes the rupture of the old one (anion-like transition state) with displacement of the leaving group [11]. The reason is that the reaction is accelerated by electron-withdrawing groups.

Electron-donor groups, on the contrary, promote the reaction (2). Therefore, it can be assumed that the elimination of the bromine anion proceeds faster than the formation of the new N–C bond. This is consistent with a lower nucleophilicity (basicity) of anilines compared to the amines we considered in [7]. In turn, low nucleophilicity of dimethylaniline is responsible for the enhanced selectivity of the reactions with alkynyl halides **2a–2c** differing in the chain length.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WM 400 instrument (solvent $CDCl_3$). The electron absorption spectra were measured on an SF-2000 spectrophotometer (cell thickness 1 cm).

Alkynyl bromides **2a–2c** were synthesized from the corresponding acetylenic alcohols and phosphorus tribromide by the procedure from [12]. *N,N*-dimethylaniline and bromides **2a–2c** were freshly distilled before use.

***N,N*-Dimethyl-N-(prop-2-yn-1-yl)anilinium bromide (3a).** A mixture of 0.32 mL (2.5 mmol) of *N,N*-dimethylaniline and 0.2 mL (2.7 mmol) of propargyl bromide was heated at 35–40°C for 2–3 min and then was allowed to stand at room temperature for 24 h. The solidified mixture was triturated three times with 0.5 mL of hexane and recrystallized from butan-1-ol. Yield 0.45 g (75%), mp 127–128°C (mp 122°C [8]).

***N*-(But-2-yn-1-yl)-*N,N*-dimethylanilinium bromide (3b)** was prepared in a similar manner from 5 mmol of *N,N*-dimethylaniline. Yield 0.95 g (73%), mp 132–133°C. ^{1}H NMR spectrum, δ, ppm: 1.65 s (3H, $\equiv CCH_3$), 3.98 s [6H, $(CH_3)_2N$], 7.45 t (1H, H^p, $J = 7.0$ Hz), 7.54 t (2H, H^m, $J = 7.5$ Hz), 8.00 d (2H, H^o, $J = 8.2$ Hz). Found, %: Br 30.82; N, 5.43. $C_{12}H_{16}BrN$. Calculated, %: Br 31.46; N 5.51.

***N,N*-Dimethyl-N-(oct-2-yn-1-yl)anilinium bromide (3c)** was prepared in a similar manner from 5 mmol of *N,N*-dimethylaniline but was not recrystallized. Yield 1.38 g (89%), mp 109–110°C. ^{1}H NMR spectrum, δ, ppm: 0.77–1.24 m (9H, $CH_2CH_2CH_2CH_3$), 1.99 t (2H, $\equiv CCH_2$), 4.03 s [6H, $(CH_3)_2N$], 5.39 s (2H, $CH_2C\equiv C$), 7.46 t (1H, H^p, $J = 7.1$ Hz), 7.56 t (2H, H^m, $J = 7.6$ Hz), 7.99 d (2H, H^o, $J = 8.3$ Hz). Found, %: Br 25.35; N 4.33. $C_{16}H_{24}BrN$. Calculated, %: Br 25.81; N 4.52.

Kinetic studies were carried out in freshly distilled acetonitrile ("for UV spectroscopy" grade) at 30°C. Initial concentrations: 0.1 (**1**), 0.165 (**2a, 2b**), 0.087 M (**2c**). To measure the amine **1** concentration over time, aliquots of the reaction mixture were diluted with acetonitrile to optical densities D_0 of 0.5–0.6. The measurements were carried out at 30–60 min intervals 6–8 times as the reaction progressed (to the extent of ≥ 50%). The rate constants (k) of the second-order reaction of amine **1** with bromides **2a–2c** were calculated by Eq. (3).

$$k = \frac{2.303}{(b-a)t} \log \frac{a(b-x)}{b(a-x)} . \tag{3}$$

Here, t is the time after the start of the reaction, min; a, initial concentration of *N,N*-dimethylaniline **1** (0.1 M); b, initial concentration of alkynyl bromide, 0.165 (**2a, 2b**), 0.087 M (**2c**); and x, concentration of the reaction product formed at time t, M.

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