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Concentration Effects in the Nucleophilic Reactions of Tertiary Amines in Aqueous Solutions. Alkylation of Amines with Ethylene Chlorohydrin

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Abstract—During the alkylation of tertiary amines with ethylene chlorohydrin in aqueous solutions, the initial rates and degrees of conversion attained within control periods of time showed nonstandard dependences on the initial concentrations of reagents. The character of the concentration dependences depended on the structure of the hydrocarbon fragments and the available sets of functional groups in amines. On the basis of our results and viscosimetric data for the model systems, we assumed that these effects were due to pre-reaction association involving the reagents and products.

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INTRODUCTION

Quaternary ammonium salts (QASs) are widely used in industry and house keeping. They are generally obtained by the Menschutkin reaction, i.e., N-alkylation of tertiary amines with haloalkyls [1]. For the reaction carried out in homogeneous aqueous solutions, the reagents should contain hydrophilic functional groups in addition to the reaction centers to ensure their high solubility. One of accessible water-soluble halogen derivatives is ethylene chlorohydrin (ECH). The products of its interactions with tertiary amines are the derivatives of choline chloride [2, 3]:

$$R_3N + ClCH_2CH_2OH \rightleftharpoons [R_3\overset{+}{N}CH_2CH_2OH]\overset{-}{Cl}. \quad (1)$$

The pre-reaction association of reagents is one of the insufficiently studied problems concerned with reactions (1) in homogeneous media. It has recently attracted more interest and was considered for different systems. The series of papers [4, 5] described a model of liquid-state reactions in associated media using the similarity in the behavior of alcohol associates with flexible-chain polymers in solutions. The model was constructed on the basis of the reactions of alcohols with isocyanates. Aminolysis of esters was the object of studies described in [6, 7]. It was shown that these processes could not be described adequately without taking into account associative interactions.

For tertiary (meth)acryl amines, it was recently shown that association of reagents in aqueous solutions produced a strong effect on both nonradical (hydrolysis of aminomethacrylates [8]) and radical (spontaneous homopolymerization of the salts of aminomethacrylates [9] and amino(meth)acrylamides [10]; initiated copolymerization of these salts with acrylamide reactions [11]. These association effects showed themselves as distinct effects of the initial concentrations of reagents inconsistent with the classical concepts. These effects were therefore expected to be also significant for nonradical nucleophilic substitution reactions of different tertiary amines in water. Importantly, studies of the concentration effects not only lead to the optimization of the reaction conditions, but also provide a method of investigating association in complex systems with multifunctional components.

The aim of this work was to study the effects of reagent concentrations on the pathway of the Menschutkin reaction of ECH and amines with different structures in aqueous solutions at low and high conversions. As amines, we mainly used reagents with $(CH_3)_2NCH_2CH_2X$ reaction centers of the same type. They are presented together with notation in the table. As is well known [12], the activity of amines in quaternization with alkyl halides primarily depends on the spatial structure and induction effects of substituents at the nitrogen atom. By varying the X substituent lying far from the amino group and containing the alcohol, nitrile, and unsubstituted or substituted amide groups, we could change the type of the intermolecular association interaction. The induction and steric factors of the reaction center did not change; this was confirmed by insignificant fluctuations in the total steric ΣR_S and induction $\Sigma\sigma^*$ constants of substituents at the amine center, determined by the

Tertiary amines used and the calculated total inductions ($\Sigma\sigma^*$) and steric (ΣR_S) constants of substituents at the amine nitrogen

R_3N	Formula	$\Sigma\sigma^*$	$-\Sigma R_S$
DE	$HOCH_2CH_2N(CH_3)_2$	0.1023	4.29
DN	$NCCH_2CH_2N(CH_3)_2$	0.3607	4.53
DA	$H_2NCOCH_2CH_2N(CH_3)_2$	0.1655	4.61
DA	$CH_2{=}CHCONH(CH_2)_3N(CH_3)_2$	0.1724	4.72
DDAA	$CH_2{=}CHCONHC(CH_3)_2CH_2CH_2N(CH_3)_2$	0.1725	5.31
DMA	$CH_2{=}C(CH_3)CONH(CH_2)_3N(CH_3)_2$	0.1726	4.95
DABCO	$N(CH_2CH_2)_3N$	–	4.43

Galkin–Cherkasov method [13, 14]. For substituents with any structure,

$$\sigma^* = \sum_{i=1}^{n} \frac{(\sigma_A)_i}{r_i^2}, \qquad (2)$$

$$R_s = 30\log\left[1 - \sum_{i=1}^{n} \frac{R_i^2}{4r_i^2}\right], \qquad (3)$$

where $(\sigma_A)_i$ is the ability of the ith atom of the substituent to show an induction effect, r_i is the distance between the ith atom and the reaction center (Å), and R_i is the covalent radius of the ith atom (Å).

The above procedure for calculating the steric and induction constants of substituents was developed for the tetracoordinated carbon atom as a reaction center. In earlier studies of the N-alkylations of tertiary amines, the use of the procedure was shown to be correct for the nitrogen atom as a reaction center as well [15].

EXPERIMENTAL

For experiments we used N,N-dimethylaminoethanol (DE), N,N-dimethylaminopropionitrile (DN), N,N-dimethylaminopropionamide (DA), N-(3-dimethylaminopropyl)methacrylamide (DMA), N-(3-dimethylaminopropyl)acrylamide (DAA), N-(1,1-dimethyl-3-dimethylaminopropyl)acrylamide (DDAA), 1,4-diazabicyclo-[2.2.2]octane (DABCO), and ECH with at least 98% main substance. The reactions of ECH with tertiary amines were carried out at 303 K (the reaction with DN was performed at 343 K); the reagents were taken in equimolar ratios. To preclude radical polymerization in the reactions of monomer amines, we introduced hydroquinone in the reaction mixtures. The Menschutkin reaction was monitored chromatographically and according to the consumption of free amino groups, determined by acid–base titration. The isolated products were identified by chemical analysis and NMR and IR spectroscopy. The specific viscosity of solutions was measured with an Ubbelode viscosimeter (the capillary diameter was chosen to be 0.34–0.99 mm) at 298 K.

RESULTS AND DISCUSSION

In the first series of experiments, we studied the effects of the structure of amines on the concentration effects in the quaternizations of tertiary amines with ECH in aqueous solutions. For all amines except DABCO (whose solubility in water restricted the possibility of obtaining high initial concentrations, over 1–2 mmol/g), we observed abrupt deceleration of the reaction. The dependences of the initial rates on the initial concentrations of reagents were determined from the kinetic data. For convenient analysis, the amines were divided into two groups: the derivatives with a functional group as an X substituent and N-(3-dimethylaminoalkyl)(meth)acrylamide monomers with a methyl substituent at the third or sixth position relative to the reaction center or without it.

The results of this study clearly showed that the concentration effects differed considerably between amines with related structures. Figure 1 shows the effect of the initial reagent concentration on the initial reaction rate for DABCO and three amines with different X acceptor substituents in the third position relative to the amine reaction center (an alcohol group in DE, nitrile in DN, and unsubstituted amide group in DA). DN was the least active of all amines used in this study over the whole range of concentrations. Its quaternization at 303 K was so slow that the temperature had to be raised to 343 K. In other nucleophilic reactions in aqueous solutions (with acrylic acid [16], or chloroacetic acid (see the next paper of this series), its activity was comparable to that of DE or DMA.

The other three amines from the first group reacted at comparable rates in dilute solutions. For DE, the initial rate increased almost linearly at higher concentrations of the starting solutions, but gradually decreased at concentrations higher than 2 mmol/g. For other amines, the reaction abruptly accelerated when the concentration increased to 0.7–1.0 mmol/g. For DABCO, the acceleration continued until the concentration reached its maximum possible level. For DA, the initial rate at first abruptly increased and then quickly decreased at concentrations of over 1.1 mmol/g. For DN, the rate also increased to a maximum (corresponding to 1.2 mmol/g) and then relatively smoothly decreased. The maximum rates varied significantly (from 29.5×10^{-4} mmol/(g min) for DE to 116.7×10^{-4} mmol/(g min) for DA).

The amines under study thus behaved differently when the initial concentrations increased in the quaternization of ECH. It is not surprising, therefore, that the differences showed themselves at high conversions as well (i.e., when the products accumulated in the systems). It was unexpected, however, that at a control synthesis time of 1.5 h, the activity of amines was quite different from the activity observed at the start of the reaction (Fig. 2). For example, at an initial concentration of 2 mmol/g the activity series was DA > DABCO > DE according to the initial rates, but DABCO > DE > DA according to the attained conversions. The dependences of conversion on the initial concentration had maxima for all amines, but the positions of the maxima were different for different reagents and strongly different from those at the initial concentrations corresponding to the highest initial rates. In the most concentrated solutions, conversions were very low, less than 2% for DA and DE and less than 4% for DN.

The differences were still more dramatic for three N-(3-dimethylaminoalkyl)(meth)acrylamides (Figs. 3 and 4). The small differences in their structure could not significantly affect the steric accessibility and electron density of the amine nitrogen (the latter was confirmed by the close pK_a values (9.23, 9.25, and 9.39 for DAA, DMA, and DDAA, respectively [17]). The dependences of the initial quaternization rates of these amines, however, were very different, although all of them passed through a maximum. For DAA, which has the least branched framework, the rate increased monotonously when the concentration increased to 2 mmol/g and then quickly decreased. The introduction of the methyl substituent in the vinyl group (DMA) led to a shift of the maximum toward low concentrations. In the narrow range of the initial concentrations 0.5–1.0 mol/g, the rate at first abruptly increased and then abruptly decreased. The maximum initial rate was similar to one attained for DAA. In highly concentrated solutions, the reaction rate was identically low for both amines.

When two methyl substituents appeared in the α position of the amide group (DDAA), the maximum rate increased nearly threefold and the corresponding concentration of reagents shifted toward large values (3 mmol/g). When the initial concentration increased to 3.15 mmol/g (i.e., only by 5%), the rate dropped by 40% and continued to do so as the concentration increased further, but still remained one order of magnitude higher than for the other two aminoamides under the same conditions.

The conversion dependences (after the control period of 1.5 h) differed substantially from the above-described dependences. The maximum conversion was attained in the least concentrated solutions for DMA, but in moderately concentrated ones for DAA and DDAA. The activity series according to the maximum conversion after 1.5 h was DDAA (48%) > DAA (34%) > DMA (16%). The conversion was minimum (less than 2.5%) in the most concentrated solutions ($c_0 \sim 4$ mmol/g).

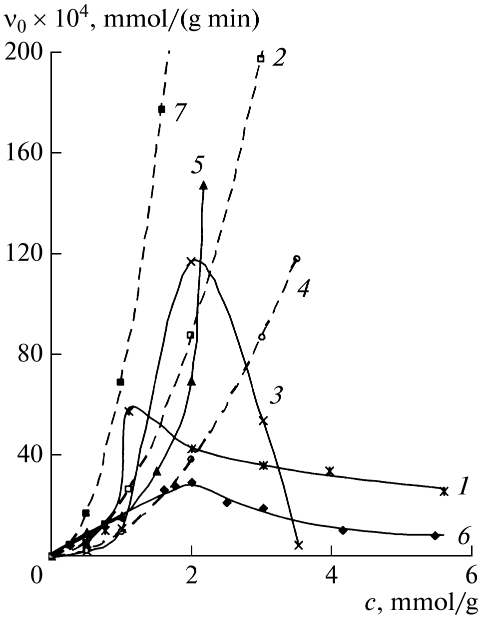

Fig. 1. Effects of the initial concentrations of reagents on the initial rates of the reactions of ECH with (*1*, *2*) DN, (*3*, *4*) DA, (*5*) DABCO, and (*6*, *7*) DE in aqueous solutions at (*3*–*7*) 303 and (*1*, *2*) 343 K. Dashed lines: calculated curves.

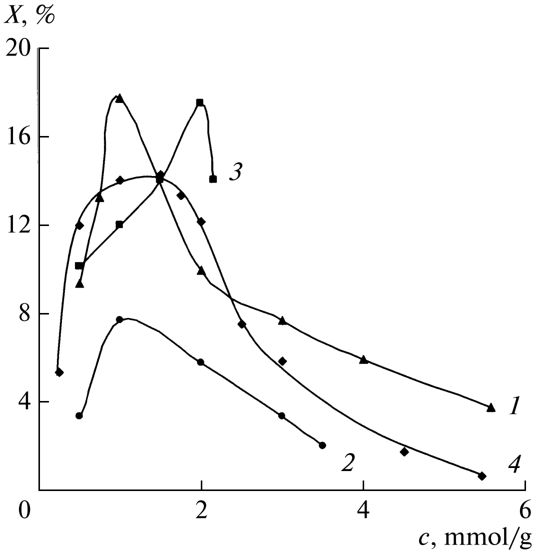

Fig. 2. Effects of the initial concentrations of reagents on the conversions in the reactions of ECH with (*1*) DN, (*2*) DA, (*3*) DABCO, and (*4*) DE in aqueous solutions at (*2*–*4*) 303 and (*1*) 343 K for 90 min.

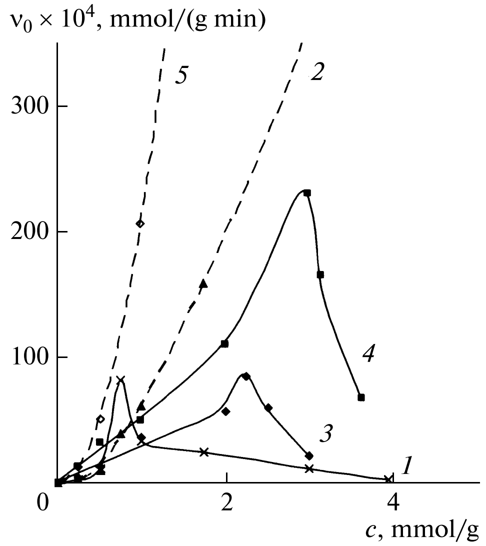

Fig. 3. Effects of the initial concentrations of reagents on the initial rates of the reactions of ECH with (*1*, *2*) DMA, (*3*) DAA, and (*4*, *5*) DDAA in aqueous solutions (303 K). Dashed lines: calculated curves.

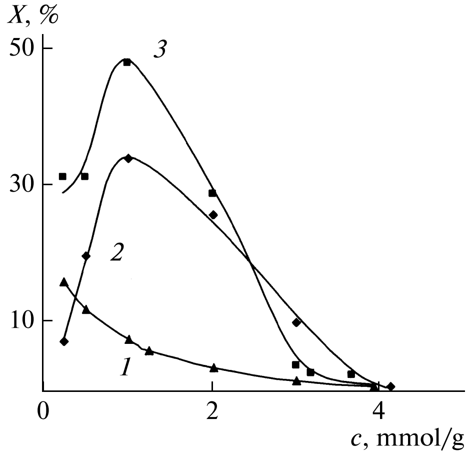

Fig. 4. Effects of the initial concentrations of reagents on the conversions in the reactions of ECH with (*1*) DMA, (*2*) DAA, and (*3*) DDAA in aqueous solutions (303 K, 90 min).

To evaluate the concentration effects more adequately, we constructed the calculated dependences of the initial rates on the concentrations of the starting reagents. Additional experiments were carried out in dilute aqueous solutions under the pseudo-first-order conditions (with a large excess of one reagent). As would be expected, the Menschutkin reaction was first-order for both reagents under these conditions. The initial rates were then determined by the second order kinetic equation for the whole range of concentrations using the rate constants found for dilute solutions. A comparison of the experimental and calculated data (Figs. 1 and 3) showed that the estimated rates were 25 to 250 times lower than those determined by the kinetic equation. For moderate initial concentrations, however, there were segments (for DA, DH, and DMA) on which the experimental initial rates markedly exceeded the calculated ones.

In constructing the calculated curves, we neglected the change in the character of the medium in different experiments. As is known, more polar media generally produce a positive effect on the Menschutkin reaction, though the character of this effect was not always unambiguous [18, 19]. The systems under study can therefore be substantially changed by reducing the mass fraction of water or by increasing the contents of less polar organic compounds (amines and ECH). We performed a series of experiments using mixtures of water and alcohol in different ratios. After the introduction of up to 40% isopropyl alcohol or ethanol into the solvent, the initial alkylation rates of different amines were reduced six- to eightfold, but did not markedly change when the alcohol fraction was increased further (Fig. 5). It follows from these data that in low and moderately concentrated solutions, the kinetically justified growth of the initial rate due to higher initial concentrations should be largely compensated by a decrease in the rate due to lower medium polarity; in more concentrated solutions, the change in polarity should not drastically lower the reaction rate.

Consequently, the inclusion of medium polarity does not decrease the discrepancy between the formally expected and real data on the concentration segments with the experimental rates higher or lower than the calculated ones. The same refers to the attained conversions and the large differences in the concentration dependences recorded in the quaternizations of tertiary amines with different structures. One logical explanation of these effects is the influence of noncovalent associations with reagents on the systems under study.

These interactions can be strongly affected even by small changes in the hydrocarbon fragments of molecules, giving rise to local regions whose composition differs substantially from the volume average. Association of organic compounds in liquid media has recently stirred the growing interest. The motive force of these interactions are noncovalent intermolecular interactions involving polar groups and nonpolar hydrocarbon fragments [20, 21]. For aqueous solutions of substances, these effects are generally considered less significant. For simple polar organic compounds (acetone, methanol, formamide), however, the possibility of forming multimolecular associates in water has been shown using novel experimental techniques and computer simulation [22]. For example, for mixtures of water with formamides in the medium range of compositions, associates can even give rise to regions with a microheterogeneous structure.

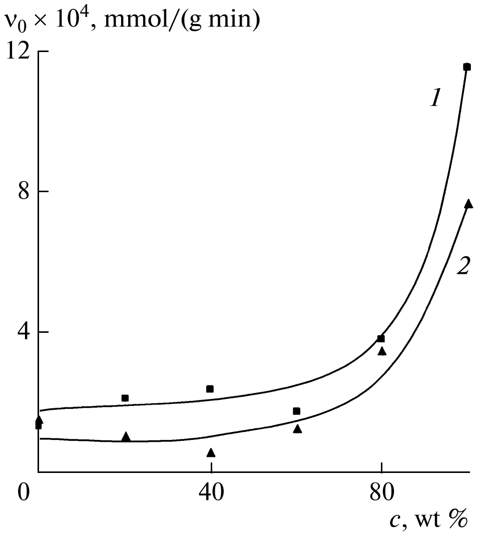

Fig. 5. Dependences of the reaction rate constants on the water content in the solvent for reactions of ECH with (*1*) DMA and (*2*) DE in (*1*) water–isopropyl alcohol and (*2*) water–ethanol mixtures at reagent concentrations of 0.5 mmol/g at 303 K.

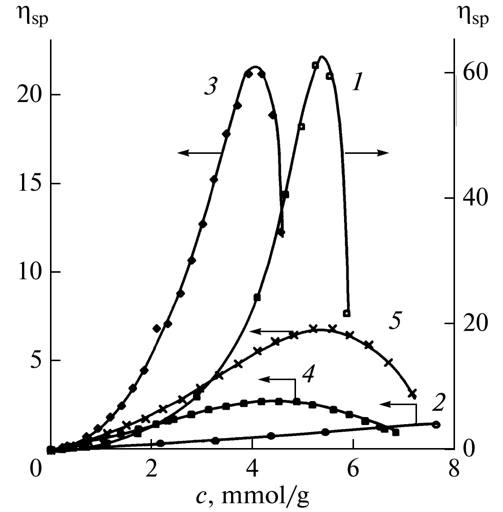

Fig. 6. Dependences of the specific viscosity on the concentrations of organic compounds for aqueous solutions of (*1*) DMA, (*2*) ethanol, (*3*) ethanol and DMA, (*4*) ethanol and DN, and (*5*) ethanol and DE at 298 K (the alcohol to amine ratio was equimolar).

Association is often confirmed by the nontrivial character of the experimental concentration dependences of the physical properties of solutions, among which viscosity is the most sensitive property [23]. We measured the specific viscosities of aqueous tertiary amines and alcohols (to avoid chemical reactions in the course of analyses, we used model systems, in which ethylene chlorohydrin was replaced with ethanol) (Fig. 6). The obtained viscosity isotherms had maxima for all compounds, as typically observed for systems with active association [23]; the concentrations of the components and viscosities corresponding to the maxima differed strongly. This can be explained by the fact that noncovalent interactions are individual for amines with different sets of functional groups or different structures of the carbon skeleton. The viscosity isotherm (Fig. 6, curve *4*) showed a smoothened maximum for a mixture of ethanol with DN (its nitrile group can form one hydrogen bond). A more distinct maximum was observed for water–ethanol solutions of DE (the hydroxyl group of the amino alcohol can form two hydrogen bonds). The most distinct maximum was found for DMA solutions (curve *3*), whose amide group contains three potential hydrogen bonding sites. For comparison, data for aqueous ethanol (curve *2*) and DMA (curve *1*) are presented. Note that the association of aminoamide in water is much stronger than in aqueous alcohol solutions.

To summarize, viscosimetric data showed that associations took place in aqueous solutions of various tertiary amines and hydroxyl-containing organic compounds (not only ECH, but also QASs). The specific character of the associations probably led to differing concentration effects in the chemical reactions. As follows from the analysis of the experimental and calculated kinetic data, there are concentration regions of “favorable” (accelerating) and “unfavorable” (decelerating) effects of association on the Menschutkin reaction in aqueous solutions. Associations can well be recorded experimentally, but the particular structures of associates in aqueous solutions of binary organic systems is a complex problem that will probably remain open to discussion for a long time, especially because they can differ substantially in solutions with different ratios of water and organic compounds. This will be treated in our next papers on the basis of other compounds.

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