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Detailing the elementary stages in the oxirane ring opening reactions with carboxylic acids catalyzed by tertiary amines

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Abstract

The study of the reaction systems " R_3N – proton-donor reagent (NuH) – epichlorohydrin" using a complex of various kinetic methods of investigation allowed the reaction pathway and the catalysis mechanism of the oxirane ring opening by proton-donor reagents in the presence of R₃N to be detailed. It was confirmed that the catalytic activity of R₃N consists in their quaternization by oxirane under the obligatory condition of its electrophilic assistance with the NuH reagent. The quaternization process of tertiary amines was studied using ¹H NMR and UV spectroscopy, quantum chemical modeling, and correlation analysis. It was shown that the transition states of the quaternization stage are dissociative, and their degree of looseness depends on the electrophilic activation of the oxirane ring.

KEYWORDS

nucleophilic catalysis, oxirane, reaction mechanism, transition state

1 INTRODUCTION

Oxiranes (epoxides) are attractive building synthons for the preparation of a variety of organic compounds with different complexity. The high activity of oxiranes is explained by the increased strain of the three-membered ring, as well as by the presence of reactive electrophilic centers-carbon atoms of the ${}^{+\delta}C-O-C^{+\delta}$ fragment. The main reactions of this class of compounds usually occur under the action of various nucleophilic proton-donor reagents (NuH) and allow one to obtain various homo- and heterofunctional derivatives, many of which are widely used in industry and everyday life. Among oxiranes, epichlorohydrin (ECH) is one of the most commercially important epoxides because its reactions with NuH reagents make it possible to both build up the carbon chain and introduce functional substituents on three neighboring C-atoms. Scheme 1 illustrates some examples of using the ECH opening reactions in the preparation of known biologically active compounds.^[1-4]

Therefore, a detailed study of such processes opens, on the one hand, ways to expanding the scope of the practical application of epoxy compounds, and on the other hand, it provides additional information on the regularities and mechanism of the oxyalkylation reaction that underlies them.

Noncatalytic oxyalkylation reactions of NuH reagents are known to have extremely low rates and are accelerated in the presence of acidic or basic catalysts. Compounds such as tertiary amines (R₃N), pyridines, and tetraalkylammonium salts are often used as the latter. Moreover, the catalytic effect of R₃N is explained in a number of cases within the framework of the mechanism of general base catalysis, [5-17] when the amine acting as the base activates the proton-donor reagent because of the transfer of its proton (Equation 1):





$$\mathbf{R}_{3}\mathbf{N} + \mathbf{N}\mathbf{u}\mathbf{H} \rightleftharpoons \mathbf{R}_{3} \overset{\dagger \delta}{\mathbf{N}} \cdots \mathbf{H} \overset{\cdot \delta}{\mathbf{N}} \mathbf{u} \rightleftharpoons \left[\mathbf{R}_{3}\mathbf{N}\mathbf{H}\right]^{+} \mathbf{N}\mathbf{u}^{-}.$$
(1)

In other cases, [17-27] the catalytic effect of amines is explained within the framework of the nucleophilic mechanism, where the amine exhibiting the properties of a nucleophile interacts with a electrophilic substrate (oxirane)^[28-32] in the trimolecular process forming an intermediate-tetraalkylammonium salt (Equation 2): system "C₆H₅NMe₂ (N,N-dimethylaniline, DMA) – AcOH (**Nu**H) – ECH," a gradual irreversible consumption of C₆H₅NMe₂³⁵ was revealed, which can correspond only to its participation in the quaternization reaction with ECH to form [R₃NCH₂CH(OH) CH₂Cl]⁺**Nu**⁻ providing the generation of the reactive anion of the proton-donor reagent (**Nu**⁻). Therefore, further interest is a deeper study of the quaternization

$$R_{3}N + \bigvee_{O} CI + NuH \longrightarrow \begin{bmatrix} R_{3}N + CI \\ OH \end{bmatrix} Nu^{-} (2)$$

The anion of proton-donor reagent (Nu^-) formed through the Equations 1 or 2 then interacts with the oxirane to form products of ECH opening $(NuCH_2CH(OH)CH_2CI$, Scheme 1, Equation 3): stage of R_3N , which explains the formation of a true catalyst in the system—the tetraalkylammonium salt, which transfers the anion of the proton-donor reagent.



But we adhere to the mechanism of transferring the anion of a nucleophilic reagent by an ion pair,³³ when the quaternary ammonium salt [$R_3NCH_2CH(OH)$ CH_2Cl]⁺ Nu^- is formed not in an elementary stage but in a complex multistage process. Confirmation of this concept is a number of experimental facts the key of which are (1) the decisive role of the nucleophilicity of R_3N rather than their basicity³³; (2) irreversible consumption of R_3X (X = N,^[34,35] P³⁶). Thus, in the In this regard, the reaction series " $ArNMe_2 - R'COOH - ECH$ ", in which the nature of both the amine and proton-donor reagent was varied, were chosen as objects of the study. To solve this problem, various methods of investigation were used: kinetic (potentiometric acid-base titration of a proton-donor reagent; UV spectroscopic determination of amine consumption), structural (UV and NMR monitoring of the initial reagents consumption), calculcations (the

quantum chemical modeling of the behavior of system components – FIREFLY 7.1.G package), and correlation analysis (establishing the relationship between changes in the structures of the starting reagents and the corresponding transition states [TSs]).

2 | EXPERIMENTAL SECTION

2.1 | Synthesis and purification of compounds

The commercially available ECH was dried during a day over sodium hydroxide granules and then distilled at atmospheric pressure collecting a fraction with a boiling point of 115–116°C; $n_{\rm D}$ 1.438 (lit. b.p. 115.5°C; $n_{\rm D}$ 1.438³⁷).

The commercially available glacial acetic acid contains impurities of carbonyl compounds that were removed by refluxing in the presence of 5% KMnO₄ solution for 1 h after which the acid was distilled over P₂O₅ to remove the residual water; b.p. 117–118°C; n_D 1.372 (lit. b.p. 118°C; n_D 1.3715³⁷). Ethoxyacetic acid was synthesized by the interaction of chloroacetic acid with sodium ethylate³⁸; ¹H NMR (400 MHz, CDCl₃): δ 1.25 (t, J = 9.1 Hz, 3H, CH₃), 3.62 (q, J = 9.2 Hz, 2H, CH₂), 4.15 (s, 2H, CH₂), 10.25 (s, 1H, COOH). 2,2-Dimethylpropanoic (pivalic) acid was synthesized according to the published methodology starting from acetone³⁹; ¹H NMR (CDCl₃): δ 1.24 (s, 9H, 3CH₃), 11.6 (s, 1H, COOH).

In order to remove the impurities of primary and secondary amines from N,N-dimethylaniline (DMA), it was refluxed for 5 h with excess of Ac₂O.³⁷ In this case, primary and secondary amines are acetylated and lose their basic character. Then most of the anhydride was distilled off, and the residue was dissolved in concentrated hydrochloric acid on cooling, and insoluble organic impurities were removed by extraction with a small amount of ether. To isolate DMA, treatment of its hydrochloride with a concentrated solution of NaOH was carried out with further distillation of the amine under reduced pressure (b.p. 105–107°C/20 mm); $n_{\rm D}$ 1.555 (lit. $n_{\rm D}$ 1.556³⁷). 4-Methoxy-*N*,*N*-dimethylaniline was obtained by methylation of p-anisidine with dimethyl sulfate⁴⁰; ¹H NMR (CDCl₃): δ 2.90 (s, 6H, 2CH₃), 3.78 (s, 3H, OCH₃), 6.86 (m, 4H, C₆H₄). 3-Nitro-N,N-dimethylaniline was synthesized by methylation of *m*-nitroaniline with methyl iodide in the presence of sodium hydride⁴¹; ¹H NMR (CDCl₃): δ 3.02 (s, 6H, 2CH₃), 6.94 (d, J = 7.9 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.47 (s, 1H), 7.55 (d, J = 7.8 Hz, 1H).

2.2 | Kinetic measurements

2.2.1 | Kinetic measurement procedure I (consumption of proton-donor reagent R'COOH)

The determination of the rate of the total reaction of ECH and R'COOH (NuH, Scheme 1) with the subsequent calculation of the observed and catalytic rate constants was based on the determination of the decrease in the concentration of the acid reagent (potentiometric acidbase titration). The solution of R'COOH of the corresponding concentration in 2 mL of ECH was introduced into one of the two compartments of the kinetic flask, and the solution of ArNMe₂ in 1 mL of ECH was added to the other. The flask was placed in the thermostat at the required temperature. After thermostating (10 min), the solutions were quickly mixed, and the flask was placed in the thermostat again. The initial time of the reaction was taken to be the mixing time of the solutions. After a necessary period of time, the reaction was stopped by adding 10 mL of a mixture of isopropyl alcohol and water (1:1 by volume) cooled to $0-5^{\circ}$ C with rapid stirring (dilution and cooling method). The contents of the flask were quantitatively transferred with distilled water to the titration cell. The current concentration of the protondonor reagent was determined by potentiometric acidbase titration with a 0.1 M NaOH solution.

2.2.2 | Kinetic measurement procedure II (consumption of ArNMe₂)

The determination of the rate of the ArNMe₂ guaternization stage and the subsequent calculation of the rate constants for the formation of the tetraalkylammonium salt were based on the determination of the concentration of the free base by UV spectroscopy. For this, at certain time intervals, the reaction mixture obtained similarly to the procedure I, after cooling in the ice bath (but without adding isopropyl alcohol) was diluted with a 10-fold excess of ECH, an aliquot was taken into a quartz cuvette (l = 1 cm) and placed in an SF-2000 spectrophotometer. The comparison solution was that of carboxylic acid in ECH previously diluted with a 10-fold excess of ECH. The consumption rate of ArNMe₂ was monitored by measuring the optical density of the reaction mixture at the optimal wavelength based on previously constructed calibration curves.

2.3 | Procedure of quantum chemical modeling

Quantum chemical calculations were performed using the PC FIREFLY 7.1.G software package.⁴² The

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construction and visualization of the structures of implemented model objects were using the ChemCraft.⁴³ The components of the system were calculated in vacuum using the density functional method (DFT) and the standard basis set $6-31 + G^{**}$. DFT calculations were performed using the B3LYP hybrid density functional. At the end of the optimization of the geometry of the structures, the calculation of rotational constants, normal vibrations frequencies, and thermodynamic functions was performed. Belonging the found TSs for the corresponding reaction was proved by the IRC descents into the valleys of reagents and products.

3 | RESULTS AND DISCUSSION

The differential equation of the rate of the total reaction (Scheme 1) is described by the Equation 4:

$$r = -\frac{\mathrm{d}C_{\mathrm{AcOH}}}{\mathrm{d}t} = \left(k_{\mathrm{non}} + k_{\mathrm{cat}}C_{\mathrm{cat}}^{x}\right)C_{\mathrm{ECH}}^{y}C_{\mathrm{AcOH}}^{z} \tag{4}$$
$$= k_{\mathrm{obs}}C_{\mathrm{ECH}}^{y}C_{\mathrm{AcOH}}^{z},$$

where k_{non} and k_{cat} are the rate constants of noncatalytic and catalytic reactions, respectively; k_{obs} is the observed reaction rate constant. The analysis of the literature shows that the order of reaction with respect to the oxirane for most of these reaction series is constant and equals to 1 (y = 1), while the order of reaction with



FIGURE 1 Kinetic curves for the reaction of acetic acid $(C^{0}_{ACOH} = 0.2 \text{ M})$ with ECH at 60°C in the presence of 4-MeOC₆H₄NMe₂ catalyst

respect to the acid reagent (z) varies depending significantly on the reaction conditions.

Based on the obtained experimental data (kinetic measurement procedure I), it was found that the kinetic curves for the consumption of acetic acid (C_{ACOH} , M) obtained at various initial concentrations of tertiary amines are linear ($r \ge 0.99$) in the coordinates $C_{ACOH} - t$ (Figure 1 for the reaction in the presence of



FIGURE 2 The dependence of the observed rate constants for the reaction of ECH with AcOH on the concentration of 4-MeOC₆H₄NMe₂ at 60°C; $C^{0}_{ACOH} = 0.2$ M; r = 0.999



FIGURE 3 UV spectra of the reaction mixture "4-MeOC₆H₄NMe₂ – AcOH – ECH" (70°C) at various time points; $C^{0}_{ACOH} = 0.3 \text{ M}; C^{0}_{amine} = 5.03 \cdot 10^{-3} \text{ M}$

4-MeOC₆H₄NMe₂). This fact corresponds to a zeroth order of reaction with respect to AcOH.

Thus, basing on the established order of the reaction with respect to AcOH (z = 0) and taking into account the excess of the oxirane (pseudo-order for ECH, y = 1), the observed rate constants were calculated using the Equation 5:

$$k_{\rm obs} = \frac{C_{\rm AcOH}^0 - C_{\rm AcOH}}{C_{\rm ECH}^0 t},\tag{5}$$

where C_{ECH}^{0} is the initial concentration of oxirane (≈ 12.5 M); *t* is the reaction time.

To establish the order with respect to the catalyst (tertiary amine), a comparison of the observed rate constants of the reaction of ECH with acetic acid and the concentration of the catalyst in accordance with Equation (6) was made:

$$k_{\rm obs} = k_{\rm non} + k_{\rm cat} C_{\rm cat}.$$
 (6)

The presence of a linear correlation (Figure 2 for 4-MeOC₆H₄NMe₂ as example) indicates the first order of reaction with respect to the catalyst (x = 1).

In accordance with Equation 6, the catalytic rate constants (k_{cat} , $M^{-1} s^{-1}$) for amines were calculated: (1.02 ± 0.03)· $10^{-4} - 4$ -MeOC₆H₄NMe₂; (0.584 ± 0.032)· $10^{-4} - C_6H_5NMe_2^{35}$; (0.104 ± 0.007)· $10^{-4} - 3$ -O₂NC₆H₄NMe₂. Moreover, the established series of catalytic activity of amines, 4-MeOC₆H₄NMe₂ ($pK_a = 5.86$) > C₆H₅NMe₂

para-position with respect to the reaction center. Thus, the revealed series of changes in k_{cat} indicates the same effect of both basicity and nucleophilicity on the catalytic activity of amines and does not allow us to differentiate which property of amines is decisive for explaining their behavior in the hydroxyalkylation of ECH.

In this regard, for further study of the potential interactions (acid-base, nucleophile-electrophile) that are possible in the reaction system and for detailing the elementary stages and TSs in the reaction pathway, the key aspect is the need to monitor the behavior of R_3N . One of the most informative methods for studying interactions in complex multicomponent systems is NMR spectroscopy. At the same time, for the case of catalytic reactions, when the amount of the catalyst (R_3N) is much less than the concentration of reagents (reaction under study: $C_{ECH} > > C_{ACOH} > > C_{R3N}$), it is impossible to carry out the indicated monitoring of the amine behavior by NMR.

Bypassing this limitation is possible using the UV spectroscopy method for the systems containing aromatic tertiary amines. The structures of substituted *N*,*N*-dimethylanilines (ArNMe₂) have characteristic features: (1) conjugation of the lone pair of electrons on the N atom with the benzene ring; (2) the disappearance of conjugation during the reaction of ArNMe₂ with various electrophiles E^+ (H⁺—amine acts as the base, R⁺—amine acts as the nucleophile) because of the participation of this electrons pair in the formation of the covalent N–E bond:



disappeared

 $(pK_a = 5.07) > 3-O_2NC_6H_4NMe_2$ ($pK_a = 2.67$), is consistent with that predicted from the basicity of amines (pK_a); that is, electron-donating substituents in the benzene ring increase the catalytic activity of ArNMe₂, and electron-withdrawing substituents decrease it.

It should be noted that the nucleophilicity of the studied tertiary amines determined jointly by the electronic and steric effects at the N atom changes in the same order as their basicity. This follows from the Hammett equation when the change in steric effect can be neglected if the substituents are varied in the meta- or The behavior of the nitrogen-containing nucleophile was monitored by this method for amines $C_6H_5NMe_2$, 4-MeOC₆H₄NMe₂, and 3-O₂NC₆H₄NMe₂. Indeed, in the UV spectra of the reaction system "ArNMe₂ – R'COOH – ECH" (Figure 3) for all studied amines a gradual decrease in the intensity of the long-wavelength absorption band corresponding to forbidden transitions due to the conjugation of the group: NMe₂ with the benzene ring was observed.

(7)

The established fact allows the reliable measurements of the concentration of free nucleophile ArNMe₂ in 6 of 14 WILEY Journal of Physical

reaction systems to be conducted on the basis of the intensity of the corresponding long-wavelength absorption band (Figure 3).

The validity of this assumption was proved by checking the fulfillment of the Bouguer–Lambert–Beer law (Figure 4 for the system "4-MeOC₆H₄NMe₂ – AcOH – ECH") at the starting time obtained at various initial concentrations of the tertiary amine.

The short-wavelength intense absorption ($\lambda \approx 250$ nm, Figure 3), corresponding to the B-band due to the allowed electronic transitions of the benzene ring, is not suitable for monitoring the concentration of free amine. This is due to the fact that both the starting compound ArNMe₂ and the product of its reaction with **E**⁺ contribute to this absorption.

Typical kinetic curves for ArNMe₂ consumption in the reaction systems with different initial concentrations of nitrogen-containing nucleophile obtained by electronic spectroscopy are presented in Figure 5.

The irreversible rather slow consumption of a free amine can only correspond to its quaternization by the oxirane molecule according to Equation 2, because the process of tertiary amines protonation (Equation 1), as a special case of the so-called barrier-free interactions, is a fairly quick reaction ($k = 10^2 - 10^3 \text{ M}^{-1} \text{ s}^{-144}$).

The reaction order with respect to $ArNMe_2$ at the stage of its quaternization by ECH was determined by the Van't Hoff method comparing the initial consumption rate of $ArNMe_2$ (the slope of the kinetic curves, Figure 5) with its initial concentration and turned out to be ≈ 1 (0.988, Equation 8, correlation coefficient 0.998).





FIGURE 5 Kinetic curves for 4-MeOC₆H₄NMe₂ consumption at different initial concentrations of amine for the quaternization stage of the reaction mixture "4-MeOC₆H₄NMe₂ – AcOH – ECH" (70°C)

$$logr_{quater}^{0} = 0.988 \cdot logC_{amine}^{0} - 1.65$$
(r = 0.998).
(8)

Thus, the ArNMe₂ consumption step is the S_N2 type reaction because its rate is directly proportional to the concentration of the nucleophilic reagent in the first degree $(r_{\text{SN2}} = kC_{\text{Nu}}C_{\text{E}}, r_{\text{SN1}} = kC_{\text{E}})$. The quaternization stage of the tertiary amine leads to the formation of the anion of the proton-donor reagent (R'COO⁻ in the case of **Nu**H = R'COOH).

The reaction systems "ArNMe₂ – AcOH – ECH" where the amine contains both electron donating and electron withdrawing substituents in the benzene ring were studied with the kinetic measurement procedure I (k_{cat} , monitoring the concentration of R'COOH) and II (k_{quater} , monitoring the concentration of ArNMe₂) in order to confirm the fact that the generation of R'COO⁻ in the reaction system is ensured precisely by ArNMe₂ quaternization and to determine the effect of this quaternization on the rate of the total reaction. Using the correlation analysis method, the obtained values of k_{quater} and k_{cat} are compared with the basicity parameters according to the Brønsted Equation 9

$$\log k = \log k^0 + \beta p K_a, \tag{9}$$

and the electronic influence of substituents according to the Hammett Equation 10:

FIGURE 4 The dependence of the optical density (A_{310}) on the concentration of 4-MeOC₆H₄NMe₂ in the reaction mixture "4-MeOC₆H₄NMe₂ – AcOH – ECH" (diluted with ECH) at the initial time point; $\varepsilon_{310} = 1130 \text{ M}^{-1} \text{ cm}^{-1}$; r = 0.998

$$\log k = \log k^0 + \rho \sigma. \tag{10}$$

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The kinetic and correlation characteristics of the reaction system "ArNMe $_2$ – AcOH – ECH" are presented in Table 1.

The following facts are noteworthy. Firstly, the negative sign of the reaction series constant ρ indicates the development of a positive charge on the reaction center-the nitrogen atom-in the TS for the consumption of ArNMe₂ in the quaternization stage during the interaction of the amine with oxirane. Secondly, the values of the corresponding constants for the reaction series— β (the sensitivity to the base properties of ArNMe₂) and ρ (the sensitivity to the electronic effects in the Ar structure)-corresponding to the opening of the ECH ring by both ArNMe₂ (k_{quater}) and the anion of the proton donor AcO⁻ (k_{cat}) differ slightly ($\beta_{quater} = 0.37$, $\beta_{\text{cat}} = 0.31; \rho_{\text{quater}} = -1.2, \rho_{\text{cat}} = -1.0$, Table 1). This indicates that the amine quaternization stage (k_{quater}) determines the observed oxirane ring opening rate (k_{cat}) and is a composite reaction of the overall process mechanism.

On the other hand, the quaternization of the amine represented by Equation 2 cannot be an elementary stage in the mechanism of the total reaction because it is trimolecular. To describe the nucleophilic opening of oxirane under the action of ArNMe₂, it is necessary to determine which of the electrophiles present in the reaction system—free oxirane (ECH, stages k_1 , k_{-1} and k_2 , Scheme 2) or bound by the proton donor (ECH·HOCOR', stages K'_1 and k'_2)—reacts with the tertiary amine.

To model the preferred nucleophile–electrophile interaction, quantum chemical calculations of the quaternization stage of $C_6H_5NMe_2$ were carried out for the paths I (Figure 6, **TS1**, electrophile—ECH) and II (Figure 6, **TS2**, electrophile—ECH·HOAc). The structural characteristics of the found TSs are presented in the Table 2.

The resulting structures and changes that occur when the nature of the electrophile (free/activated oxirane) varies in **TS1** and **TS2** for S_N reactions (including the ArNMe₂ quaternization with the oxirane) can be conveniently described using the two-dimensional reaction coordinate—the More O'Ferrall–Jencks diagram⁴⁶ (Figure 7). Along the axes, the diagram reflects the dynamics of key processes that occur during the nucleophilic substitution at a saturated carbon atom: top-down movement—the formation of the bond between the

TABLE 1 Kinetic and correlation characteristics of the reaction system "ArNMe₂ – AcOH – ECH" (σ —Hammett constant of the substituent)

ArNMe ₂	pK _a	σ^{45}	$k_{\rm quater} \cdot 10^4$ (70°C), $M^{-1} s^{-1}$	$k_{\rm cat}$ ·10 ⁴ (60°C), M ⁻¹ s ⁻¹
MeO	5.86	-0.268	19.7	1.02 ± 0.03
NMe ₂	5.07	0	6.11	0.584 ± 0.032
NMe ₂ O ₂ N	2.67	0.71	1.07	0.104 ± 0.007
Correlation parameters			$\beta_{\text{quater}} = 0.37 \ (r = 0.984)$	$\beta_{\rm cat} = 0.31 \; (r = 0.999)$
			$ \rho_{\text{quater}} = -1.2 \ (r = 0.989) $	$\rho_{\rm cat} = -1.0 \ (r = 0.999)$



SCHEME 2 Possible ways of quaternization of tertiary amine with oxirane



FIGURE 6 Structures of the transition states TS1 (path I) and TS2 (path II, electrophilic assistance by acetic acid) calculated in the B3LYP/6-31 + G** approximation for the gas phase

TABLE 2 TSs geometric parameters (bond length *l*, angle \angle , bond order n^{\neq}) and imaginary frequency values (i ν) in the vibrational spectrum of transition states for the paths **I** (**TS1**) and **II** (**TS2**)

		l, Å				∠, °				n≠	
TS	$-i\nu$, cm ⁻¹	N^1C^2	C^2O^1	C ¹ O ¹	C^1C^2	$\overline{O^1C^1C^2}$	$C^1 C^2 N^1$	$O^1 C^2 N^1$	$0^1 C^1 C^2 N^1$	$\overline{C^2O^1}$	C^2N^1
1	264	1.780	2.119	1.339	1.537	94.7	125.7	164.6	-177.7	0.294	0.467
2	411	2.045	1.942	1.390	1.488	84.8	119.9	164.4	-173.5	0.409	0.325



FIGURE 7 Two-dimensional reaction coordinate of the ECH opening by $C_6H_5NMe_2$ molecule (Scheme 3) upon varying the nature of the electrophilic component (free/activated oxirane)

nucleophile and the electrophilic center (N–C bond order n^{\neq}_{C2N1} , Table 2), horizontally left to right—bond breaking between the electrophilic center and the leaving

group in the oxirane (C–O bond order n^{\neq}_{C2O1}). The upper left (**A**) and lower right (**D**) angles are the valleys of the starting reagents and the quaternization product, respectively, with the diagonal **AD** describing the path of the synchronous $S_N 2$ mechanism (an analog of the onedimensional coordinate). The two remaining angles show the position of the intermediates for the limiting variants of the nucleophilic substitution reaction: The angle **B** is for the $S_N 1$ mechanism (includes carbocation, path **ABD**), and the angle **C** is for the $S_A N$ mechanism (includes a hypothetical intermediate with a fivecoordinated carbon atom, path **ACD**).

The diagram shows the positions of the TSs for the quaternization of DMA by a molecule of free ECH (**TS1**) and protonated with acetic acid (**TS2**) according to the results of quantum chemical modeling (Table 2). It follows from the diagram that both TSs are dissociative because the degree of C–O bond cleavage prevails over the degree of C–N bond formation.

To predict the displacement of the TS in the More O'Ferrall–Jencks two-dimensional reaction coordinates, it is convenient to be guided by the Hammond postulate (the shift of the TS along the main diagonal of the reaction **AD** occurs to an angle that increases in energy or from an angle whose free energy decreases) and the Thornton rule (the TS shift occurs perpendicular to the diagonal **AD** to the angle whose energy decreases or from the angle with increased energy).⁴⁶ The observed total TS shift is described by the sum of the displacement vectors parallel and perpendicular to the **AD** diagonal.

Analyzing the positions of the TSs, it can be seen that path **II**, which involves the activation of the oxirane by the proton-donor reagent, is characterized by an earlier and more dissociative TS (**TS2**). Paths **I** and **II** differ in the structure of particles containing an opened oxirane ring (angles **B** and **D**, Scheme 3).

From Scheme 3, it is obvious that the free energies of the angles **B** and **D** in the case of path **II** will be much lower than for **I**, because the neutral alcohol molecule is thermodynamically more stable than the corresponding alcoholate, and ROH is a better leaving group than RO⁻. Then, taking into account the Hammond postulate and the Thornton rule, the sum of the perpendicular and parallel to **AD** vectors really describes the observed resulting displacement **TS1** \rightarrow **TS2** (Figure 7), which fits the results of quantum chemical modeling.

The calculated activation parameters for **TS1** and **TS2** are shown in Table 3.

According to the data obtained, in the case of the DMA nucleophile, path **II** (electrophilic assistance with the acid reagent CH₃COOH (**TS2**)) is characterized by a significant decrease in the activation energy (E_a) and by an increase in the rate constant for the opening of oxirane (k), that is, is preferred over the path **I**.

To experimentally establish the preferred path of the quaternization reaction, the effect of varying the initial concentration of the acid reagent on its rate was studied (Figure 8).

The obtained kinetic curves of the consumption of ArNMe₂ show that the initial reaction rate (r^0_{quater}) increases with rising the initial concentration of acetic acid.

A comparison of the initial consumption rate of ArNMe₂ (log r^{0}_{quater}) with the initial acid concentration (log r^{0}_{quater}) shows (Equation 11) that the reaction order with respect to AcOH is ≈ 1 (the tangent of the straight line) at the stage of quaternization:

$$log r_{quater}^{0} = 1.003 \cdot log C_{AcOH}^{0} - 3.21$$
(11)
(12)

Therefore, the experimental kinetic equation for the stage of opening the oxirane ring by the amine is described by the Equation 12:

$$r_{\text{quater}} = k_{\text{exp}} C_{\text{amine}} C_{\text{R'COOH}}.$$
 (12)

To establish the correspondence of the obtained kinetic equation to paths I and/or II, Scheme 2 was analyzed



TABLE 3 Standard activation thermodynamic parameters (ΔH^{\neq} , ΔS^{\neq} , ΔG^{\neq}), activation energy (E_a), and reaction rate constants (k) calculated in the B3LYP/6-31 + G^{**} approximation for gas phase

TS	Path	$\Delta H^{ eq}$, kJ/mol	ΔS^{\neq} , kJ/mol·K	$\Delta G^{ eq}$, kJ/mol	<i>E</i> _a , kJ/mol	k, s^{-1}
1	Ι	145.7	-40.21	157.7	142.9	$1.47 \cdot 10^{-15}$
2	II	78.70	-89.71	105.5	83.96	$2.08 \cdot 10^{-6}$



FIGURE 8 Kinetic curves for 4-MeOC₆H₄NMe₂ consumption at different initial concentrations of the acid reagent of the reaction mixture "4-MeOC₆H₄NMe₂ – AcOH – ECH" (70°C)

using approximate kinetic methods. For the path II, when the tertiary amine attacks the protonated ECH, the rate of the quaternization stage (ArNMe₂ consumption) is described by the Equation 13:

$$r_{\text{quater}} = k_2^{'} C_{\text{ECH} \cdot \text{HOCOR}} C_{\text{amine}}.$$
 (13)

The concentration of the oxirane activated by the acid, according to the principle of quasi-equilibrium concentrations, is described by the Equation 14:

$$C_{\text{ECH}\cdot\text{HOCOR}'} = K_1' C_{\text{ECH}} C_{\text{R}'\text{COOH}}.$$
 (14)

Given the Equations 13 and 14, the expression for the rate of quaternization takes the form:

$$r_{\text{quater}} = k_2 K_1 C_{\text{ECH}} C_{\text{R'COOH}} C_{\text{amine}}, \qquad (15)$$

which is in full agreement with the experimental results (Equation 12), because it corresponds to the first order of the reaction with respect to both the proton donor and amine, and $k_{exp} = k'_2 K'_1 C_{ECH}$.

For path **I**, when the amine attacks nonactivated ECH, the quaternization rate is described by the Equation 16:

$$r_{\text{quater}} = k_2 C_{\text{alcoholate}} C_{\text{R'COOH}}.$$
 (16)

Given the principle of stationarity, the concentration of unstable intermediate alcoholate could be found from Equations 17 and 18:

$$\frac{\mathrm{d}C_{\mathrm{alcoholate}}}{\mathrm{d}t} = k_1 C_{\mathrm{ECH}} C_{\mathrm{amine}} - k_{-1} C_{\mathrm{alcoholate}} \qquad (17)$$
$$-k_2 C_{\mathrm{alcoholate}} C_{\mathrm{R'COOH}} = 0,$$

$$C_{\text{alcoholate}} = \frac{k_1 C_{\text{ECH}} C_{\text{amine}}}{k_{-1} + k_2 C_{\text{R'COOH}}}.$$
 (18)

Substituting Equation 18 (for $k_2 > > k_{-1}$) into (16), the Equation 19 is obtained:

$$r_{\text{quater}} = k_1 C_{\text{ECH}} C_{\text{amine,}} \tag{19}$$

which corresponds to the zeroth order of the reaction with respect to the proton-donor reagent and contradicts the experimental results.

Alternatively, the answer to the question about the experimentally feasible reaction path was obtained by comparing the dependence of the initial rate of the DMA quaternization step (log k_{quater}) on the acidity of the proton-donor reagent (p K_a). For this, the reaction systems "C₆H₅NMe₂ – trimethylacetic acid (p $K_a = 5.03$) – ECH" and "C₆H₅NMe₂ – ethoxyacetic acid (p $K_a = 3.60$) – ECH" with various parameters of p K_a of the reagent were studied additionally by means of electronic spectroscopy (Kinetic measurement procedure II). In accordance with the Brønsted equation for acids—Equation 20,

$$\log k = \log k^0 - \alpha p K_a, \qquad (20)$$

it has been established that the rate constants of DMA quaternization by ECH in the " $C_6H_5NMe_2 - R'COOH - ECH$ " systems are well correlated with the acidity parameters of the reagent (Equation 21):

$$logk_{quater} = 1.0 - 0.51pK_a$$
(r = 0.995, N = 3). (21)

This suggests that acids with both electron-donating and electron-withdrawing substituents act by a single mechanism and confirm the participation of the proton-donor reagent in the quaternization stage. An increase in the acidic properties of carboxylic acid leads to an increase in the rate of quaternization, similar to rising C_{ACOH}^0 in the reaction system "4-MeOC₆H₄NMe₂ – AcOH – ECH" (Figure 8). The slope of the straight line ($\alpha = 0.51$, Equation 21) indicates a significant degree of H⁺ transfer in the TS of the quaternization stage, because, otherwise, a linear correlation either would not be observed or would

be characterized by low sensitivity to the proton donor acidity ($\alpha < 0.1^{46}$).

The results of UV spectroscopic studies and correlation analysis of the quaternization stage of tertiary amines in the reaction series "ArNMe₂ – AcOH – ECH" (β = 0.37, Table 1) and "C₆H₅NMe₂ – R'COOH – ECH" (α = 0.51, Equation 21) indicate the greater sensitivity of the quaternization rate constant to the strength of the acid reagent R'COOH and, therefore, to the nature of the leaving group than to the nucleophilicity of ArNMe₂ ($\alpha > \beta$). This is in favor of dissociative TS. Thus, the conclusion about the dissociative nature of the TS of the amine quaternization stage obtained by experimental methods is completely consistent with the data of quantum chemical modeling (Table 2, Figure 7).

UV spectroscopy as noted above is not suitable for confirming the occurrence of the quaternization stage in the case of aliphatic tertiary amines (there is no



FIGURE 9 ¹H NMR spectrum of the mixture of ECH and Et₃N (1:2, CDCl₃, 400 MHz)



FIGURE 10 ¹H NMR spectrum of the mixture of ECH, Et_3N , and AcOH at the initial time point (CDCl₃, 400 MHz)

FIGURE 11 ¹H NMR spectrum of the mixture of ECH, Et₃N, and AcOH after heating for 2 h at 60°C (CDCl₃, 400 MHz)



characteristic chromophore). For this purpose, ¹H NMR spectroscopy was used to analyze the "Et₃N – ECH" (Figure 9) and "ECH – AcOH – Et₃N" mixtures (Figures 10 and 11) with comparable concentrations of reacting substances at different time intervals. The assignment of signals from diastereotopic protons of ECH was carried out according to the spectral database.⁴⁷

In the case of the system " $Et_3N - ECH$ " (Figure 9), the observed δ values of the triplet from the CH₃ group (H(6), 1.02 ppm) and the quadruplet from the CH₂ group of Et₃N (H(5), 2.51 ppm) practically coincide with the literature data for a solution of Et₃N in CDCl₃⁴⁷ (0.97 and 2.43 ppm, respectively) and, therefore, belong to the free base molecule. When acetic acid is added to the mixture at the initial time point (Figure 10), the position of the ECH signals remains unchanged, while the CH₃ and CH₂ signals of the triethylamine protons are shifted to the weaker field by 0.2 and 0.5 ppm, respectively (signals H(6')) and H(5')). Such deshielding can be explained by the binding of the tertiary amine with the acid reagent (Equation 1), which leads to the appearance of a positive charge on the N atom. It is noteworthy that, because of the development of a partial negative charge on the O atom, the singlet of the CH₃ group of acetic acid (H(7), δ 1.97 ppm), on the contrary, slightly shifts to a stronger field (in the acetic acid itself δ CH₃ is 2.1 ppm⁴⁷).

Heating the mixture "Et₃N – AcOH – ECH" at 60° C for 2 h (Figure 11) leads to three key changes in the ¹H NMR spectrum of the initial reaction system. Firstly, a singlet appears at 2.1 ppm, corresponding to

the products of the ECH opening under the action of AcO⁻ (chlorohydrin ester of acetic acid, Scheme 1 and Equation 3 (NuCH₂CH(OH)CH₂Cl, Nu = AcO)). Secondly, a new triplet is formed at δ 1.34 ppm. Obviously, the source of the indicated triplet in this range of δ can be only the methyl group in the CH₃-CH₂-N⁺ fragment. Increasing the intensity of the new triplet over time, which was observed experimentally, can be explained only by the gradual quaternization of Et₃N and the formation of tetraalkylammonium carboxylate, which was initially absent in the reaction system. Finally, the complication of the character and the appearance of new signals in the region of 3-5 ppm, a gradual decrease in the intensity of the multiplets of the initial oxirane (signals H(1), H(2), H(3)), is due to the opening of the ECH ring under the influence of nucleophiles present in the reaction system: Et₃N (initial) and AcO⁻ (formed as a result of Et₃N quaternization).

Finally, in order to elucidate the role of the acid reagent on the interaction of ECH with amine, the two-component system "Et₃N – ECH," which does not contain acetic acid, was studied by ¹H NMR method. Heating this mixture at 60°C (1 h) practically does not lead to any changes in the spectrum where the signals of the initial amine and oxirane remained unchanged, in contrast to the results shown in Figure 11, where Et₃N and ECH were consumed simultaneously accompanied by the accumulation of reactions products. Thus, the presence of a proton donor is a prerequisite for the possibility of nucleophilic opening of the oxirane ring by aliphatic tertiary amines (as in the case of ArNMe₂).

4 | CONCLUSIONS

Detailing the nucleophile-electrophile interactions in the systems "R₃N - NuH - oxirane" was carried out with experimental and theoretical methods. It was found that in the reaction under investigation, the activation of the oxirane by the proton-donor reagent is carried out; the tertiary amine is consumed in the quaternization stage reacting with the activated oxirane according to the S_N2 mechanism with the formation of tetraalkylammonium carboxylate. The salt thus formed serves as a true catalyst for the subsequent stage of the oxirane ring opening by NuH leading to the formation of chlorohydrin esters. The quaternization of tertiary amines under reaction conditions was first studied by ¹H NMR and UV spectroscopy. Using the methods of quantum chemical modeling and correlation analysis, it was shown for the first time that the TSs of the quaternization stage are dissociative, their degree of looseness increasing upon the activation of the oxirane ring by the NuH reagent.

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