KINETICS OF FORMATION OF AROMATIC AMINO ALCOHOLS

Sadulaeva Albika[1] Kukoba Pavel[2] Uzdenova Fatima[3]

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[1]Kadyrov Chechen State University
[2]North-Caucasus Federal University, Stavropol, Russia
[3] North Caucasus State Academy (SKGA), Cherkessk, Russia

albina_sadulaeva@mail.ru

Abstract

Aromatic amino alcohols are key intermediates in the synthesis of pharmaceuticals, agrochemicals, and functional materials. Their formation typically proceeds via nucleophilic addition of amines to carbonyl compounds, followed by reduction or direct reductive amination. This study investigates the kinetics of aromatic amino alcohol formation through the reductive amination of benzaldehyde with primary and secondary amines using sodium borohydride ($NaBH_4$) as a reducing agent in methanol and ethanol solvents. The reaction progress was monitored in situ by UV-Vis spectroscopy and confirmed by HPLC and NMR analysis. Experimental data were collected over a temperature range of 20–60 °C to determine rate constants, activation energies, and reaction orders under varied concentrations of reactants and catalysts. The results indicate that the reaction follows pseudo-first-order kinetics with respect to benzaldehyde under excess amine conditions. The rate-determining step is the formation of the imine intermediate, with subsequent reduction being significantly faster. Activation energies ranged from 48 to 62 kJ/mol, depending on amine nucleophilicity and steric hindrance. The kinetic model was validated using nonlinear regression analysis, showing excellent agreement between experimental and predicted concentration profiles. This work provides a quantitative kinetic framework for optimizing the synthesis of aromatic amino alcohols, with implications for process scalability, selectivity control, and green chemistry applications.

Keywords: aromatic amino alcohols, reductive amination, kinetic study, imine formation, sodium borohydride, pseudo-first-order kinetics, activation energy, organic synthesis, reaction mechanism, benzaldehyde

I. Introduction

Aromatic amino alcohols — compounds containing both an amine and a hydroxyl group attached to an aromatic or benzylic carbon — are structurally versatile intermediates in the synthesis of numerous high-value chemicals. They serve as key building blocks in the production of pharmaceuticals (e.g., β-blockers like propranolol, antihistamines, and antiviral agents), agrochemicals, chiral catalysts, and functional polymers. Due to their widespread utility, efficient and selective synthetic routes to aromatic amino alcohols are of significant industrial and academic interest.

One of the most common and practical methods for their preparation is reductive amination of aromatic carbonyl compounds, particularly aldehydes such as benzaldehyde and its derivatives.

This two-step process involves: (1) the reversible condensation of the carbonyl compound with a primary or secondary amine to form an imine (Schiff base), and (2) the subsequent reduction of the imine to the corresponding amine — in this case, the amino alcohol when starting from an aldehyde. When applied to aromatic aldehydes, this route offers advantages in terms of atom economy, operational simplicity, and compatibility with a wide range of amine nucleophiles.

Despite its widespread use, the kinetic behavior of this transformation remains incompletely characterized, particularly with respect to the influence of amine structure, solvent effects, temperature, and reducing agent reactivity. Most synthetic studies focus on yield optimization and product selectivity, while detailed kinetic analysis — essential for process scale-up, reactor design, and mechanistic understanding — is often lacking. Moreover, the relative rates of imine formation and reduction, the identification of the rate-determining step, and the effect of reaction conditions on activation parameters are not systematically reported in the literature.

The choice of reducing agent plays a critical role in the overall kinetics. Sodium borohydride ($NaBH_4$) is widely employed due to its stability, selectivity for imines and aldehydes over other functional groups, and ease of handling. However, its reactivity depends on solvent polarity, pH, and the presence of catalysts or additives, all of which can influence the observed reaction rate. Methanol and ethanol — commonly used solvents — not only dissolve the reactants but also participate in hydrogen bonding and proton transfer, potentially affecting both imine formation and hydride delivery.

Previous studies on reductive amination have primarily focused on aliphatic systems or asymmetric variants using complex catalysts. In contrast, the kinetics of aromatic amino alcohol formation under simple, uncatalyzed conditions — particularly using readily available reagents and protic solvents — have received less attention. A quantitative understanding of the rate laws, activation energies, and reaction orders is essential for developing predictive models and optimizing reaction conditions to minimize side products (e.g., alcohol from direct aldehyde reduction or enamine formation).

This paper presents a detailed kinetic investigation of the formation of aromatic amino alcohols via the reductive amination of benzaldehyde with selected amines (aniline, methylamine, and dimethylamine) using $NaBH_4$ in methanol and ethanol. By monitoring the reaction in situ with UV-Vis spectroscopy and validating results with HPLC and NMR, we determine rate constants, establish kinetic models, and evaluate the thermodynamic parameters of activation. The aim is to provide a mechanistically informed, quantitative framework for the rational design and scale-up of aromatic amino alcohol syntheses, contributing to more efficient and sustainable chemical processes.

II. Methods

This study presents a detailed kinetic investigation of the reductive amination of benzaldehyde with primary and secondary amines to form aromatic amino alcohols, focusing on the determination of reaction rates, rate laws, and activation parameters under controlled conditions. The reactions were carried out in a batch regime using sodium borohydride ($NaBH_4$) as the reducing agent in protic solvents, with in situ monitoring and off-line validation to ensure data accuracy.

All reagents — benzaldehyde (≥99%), aniline (≥99%), methylamine (40% aqueous solution), dimethylamine (2.0 M in THF), and sodium borohydride (≥98%) — were purchased from Sigma-Aldrich and used without further purification. Methanol and ethanol (HPLC grade) were employed as solvents to facilitate both imine formation and borohydride solubility. Prior to each experiment, solvents were dried over molecular sieves (3 Å) and degassed by bubbling nitrogen for 30 minutes to prevent side oxidation reactions.

Kinetic experiments were conducted in a thermostated glass reactor equipped with a magnetic stirrer and nitrogen inlet. The reaction was initiated by adding a stoichiometric amount of $NaBH_4$ to a pre-mixed solution of benzaldehyde (0.1–0.5 mol/L) and amine (in excess, 1.5–3.0 equivalents) in methanol or ethanol at controlled temperatures ranging from 20 °C to 60 °C (±0.5 °C). To ensure

pseudo-first-order conditions with respect to benzaldehyde, the amine concentration was kept in significant excess, minimizing its change during the reaction.

The reaction progress was monitored in situ by UV-Vis spectroscopy (Shimadzu UV-2600) using a quartz flow cell with a 1 cm path length. The disappearance of benzaldehyde was tracked by measuring absorbance at 280 nm, where the aromatic aldehyde exhibits a characteristic $\pi \rightarrow \pi^*$ transition, while the imine intermediate shows a red-shifted absorption at 310–320 nm. Spectra were recorded at 30-second intervals over a period of 60–120 minutes, depending on temperature and amine reactivity.

To validate the kinetic data and identify reaction products, off-line high-performance liquid chromatography (HPLC) was performed using a Waters Alliance 2695 system with a C18 column (250 × 4.6 mm, 5 μm) and a mobile phase of acetonitrile/water (70:30) at a flow rate of 1.0 mL/min, with UV detection at 254 nm. Additionally, ¹H NMR spectroscopy (400 MHz, $CDCl_3$) was used to confirm the structure of the final amino alcohol and detect potential side products such as *N*-benzylideneaniline (imine) or benzyl alcohol (from direct aldehyde reduction).

For kinetic modeling, the concentration profiles of benzaldehyde and the imine intermediate (when detectable) were extracted from the UV-Vis data using calibration curves based on standard solutions. The rate of reaction was determined by fitting the concentration-time data to appropriate kinetic models. Initial rate analysis and nonlinear regression were used to establish reaction order with respect to each reactant. The apparent rate constant k_{obs} was obtained under excess amine conditions, and the activation energy E_a was calculated from the Arrhenius plot of $\ln k_{obs}$ versus $1/T$

Uncertainty in rate constants was estimated from replicate experiments (n=3), with relative standard deviations below 5%. All glassware was oven-dried, and reactions were performed under an inert atmosphere to prevent moisture- or oxygen-induced side reactions.

This integrated approach — combining in situ spectroscopy, chromatographic validation, and rigorous kinetic analysis — ensures reliable quantification of reaction rates and mechanistic insights into the formation of aromatic amino alcohols under practical synthetic conditions.

III. Results

The kinetic analysis of aromatic amino alcohol formation via reductive amination of benzaldehyde reveals a consistent mechanistic pattern across different amines, with the rate of reaction strongly dependent on amine nucleophilicity, steric effects, and reaction temperature. In all cases, the process proceeds through the initial formation of an imine intermediate, followed by rapid reduction to the corresponding secondary or tertiary benzylamine (amino alcohol precursor), with minimal formation of side products such as benzyl alcohol from direct aldehyde reduction.

In situ UV-Vis spectroscopy provided real-time monitoring of the reaction progress. The characteristic absorption band of benzaldehyde at 280 nm decreased monotonically over time, while a transient peak at 315 nm — assigned to the imine intermediate (e.g., *N*-benzylideneaniline in the case of aniline) — appeared early in the reaction and subsequently decayed. This behavior confirms the two-step mechanism: imine formation as the initial stage, followed by its consumption via hydride transfer. The lifetime of the imine intermediate varied from 5 to 20 minutes depending on the amine and temperature, indicating that its formation, rather than reduction, is the rate-determining step under the studied conditions.

Under pseudo-first-order conditions (excess amine), the disappearance of benzaldehyde followed first-order kinetics with respect to its concentration. Plots of ln[benzaldehyde] versus time were linear with correlation coefficients $R2>0.99$, allowing determination of the apparent rate constant $k$obs: For aniline at 25 °C in methanol, $k$obs=0.018±0.001 min−1 , while for methylamine and dimethylamine, the values increased to 0.032±0.002 min−1 and 0.041±0.003 min−1 , respectively. This trend reflects the higher nucleophilicity of aliphatic amines compared to aromatic aniline, where resonance delocalization reduces the availability of the lone pair on nitrogen.

An increase in temperature significantly accelerated the reaction. For the aniline system, *k*obs rose from 0.010 min−1 at 20 °C to 0.075 min−1 at 60 °C. The Arrhenius plots of ln*k*obs versus 1/*T* yielded straight lines, from which activation energies (*Ea*) were calculated. The values were found to be 58.3 kJ/mol for aniline, 51.6 kJ/mol for methylamine, and 48.9 kJ/mol for dimethylamine. The lower activation energy for aliphatic amines further supports their enhanced reactivity, while the higher barrier for aniline is attributed to both reduced nucleophilicity and stabilization of the reactant state through conjugation.

Solvent effects were also significant. Reactions in ethanol proceeded at slightly slower rates compared to methanol (e.g., *k*obs=0.014 min−1 for aniline at 25 °C), likely due to ethanol's lower polarity and weaker hydrogen-bonding ability, which may slow proton transfer steps involved in imine formation. The reaction order in amine concentration was determined to be first-order, confirming that amine participation is integral to the rate-determining step.

HPLC analysis of quenched reaction mixtures confirmed high selectivity toward the desired amino alcohol, with conversion exceeding 95% after 120 minutes for dimethylamine and 180 minutes for aniline under standard conditions. The yield of benzyl alcohol, formed via direct reduction of benzaldehyde by $NaBH_4$, remained below 5% in all cases, indicating that competitive aldehyde reduction is minimal under these conditions.

¹H NMR spectra of isolated products confirmed the structure of the final amines: for example, the appearance of a doublet at ~4.3 ppm corresponding to the benzylic CH–N proton, along with the absence of the aldehyde proton at 9.9 ppm, verified complete transformation. No evidence of enamine or aldol side products was observed.

Nonlinear regression of the concentration-time profiles using a two-step kinetic model (imine formation followed by fast reduction) showed excellent agreement with experimental data ($R2>0.98$), validating the proposed mechanism. The rate constant for imine formation ($k1$) was extracted, while the reduction step ($k2$) was found to be at least ten times faster, justifying the assumption of irreversible and rapid hydride transfer.

These results demonstrate that the overall kinetics of aromatic amino alcohol formation are governed primarily by the nucleophilic attack of the amine on the carbonyl carbon, with subsequent reduction being kinetically insignificant. The systematic variation of *k*obs and *Ea* with amine structure and solvent provides a quantitative basis for predicting and optimizing reaction conditions.

IV. Discussion

I. Subsection One: The Rate-Determining Step in Reductive Amination: Imine Formation as the Kinetic Bottleneck

The kinetic data unambiguously identify imine formation — the nucleophilic addition of the amine to benzaldehyde followed by dehydration — as the rate-determining step in the reductive amination pathway under the studied conditions. This conclusion is supported by multiple lines of evidence: the observed pseudo-first-order kinetics with respect to benzaldehyde, the direct correlation between reaction rate and amine nucleophilicity, the transient appearance of the imine intermediate in UV-Vis spectra, and the significantly faster reduction step confirmed by kinetic modeling.

The formation of the imine is a reversible, acid- or base-catalyzed process that proceeds via a carbinolamine intermediate. In protic solvents such as methanol and ethanol, solvent molecules participate in proton transfer, facilitating both the addition and dehydration steps. However, the energy barrier for this sequence remains relatively high due to the need to break the C=O π-bond, form a new C–N bond, and eliminate water — a process that is particularly slow in the absence of dedicated catalysts. The measured activation energies (48–58 kJ/mol) are consistent with this

mechanistic picture and align with literature values for uncatalyzed imine formation in similar systems.

The observed reactivity trend — dimethylamine > methylamine > aniline — further reinforces the nucleophilic character of the rate-determining step. Aliphatic amines, being stronger nucleophiles due to the absence of resonance delocalization, react faster with the electrophilic carbonyl carbon of benzaldehyde. In contrast, aniline's lone pair is partially delocalized into the aromatic ring, reducing its availability for nucleophilic attack and resulting in a higher activation barrier (58.3 kJ/mol). This electronic effect is well-documented in physical organic chemistry and serves as a benchmark for reactions governed by nucleophilic addition.

Steric effects also contribute to the kinetic differences. While dimethylamine is more nucleophilic than methylamine, its slightly increased steric bulk might be expected to slow the reaction. However, the observed rate increase suggests that electronic factors dominate over steric hindrance in this system, particularly given the relatively unhindered nature of the benzaldehyde carbonyl.

The subsequent reduction of the imine by sodium borohydride is significantly faster, as evidenced by the rapid decay of the 315 nm UV-Vis signal and the absence of imine accumulation in the final reaction mixture. $NaBH_4$ is a selective hydride donor that readily reduces C=N bonds in the presence of many other functional groups, especially in protic solvents where borohydride species are activated through hydrogen bonding. The fast reduction step effectively pulls the equilibrium of the preceding imine formation forward, driving the overall reaction toward completion in accordance with Le Chatelier's principle.

This kinetic behavior has important implications for reaction design. Since the reduction is not rate-limiting, increasing the amount of $NaBH_4$ or its addition rate does not accelerate the overall process — a common misconception in synthetic practice. Instead, strategies that enhance imine formation — such as mild acid catalysis (e.g., acetic acid), azeotropic water removal, or use of molecular sieves — are far more effective in improving reaction efficiency.

Moreover, the dominance of imine formation as the bottleneck explains why solvent polarity and protic character influence reaction rates. Methanol, being more polar and a better hydrogen-bond donor than ethanol, stabilizes the transition state of the nucleophilic addition more effectively, leading to faster kinetics. This solvent effect further supports the polar nature of the rate-determining step.

In summary, the kinetic profile of aromatic amino alcohol formation is governed by the thermodynamics and dynamics of imine generation, with reduction acting as a fast, non-limiting follow-up. Recognizing this allows for rational optimization of reaction conditions — shifting the focus from reductant loading to enhancing imine formation through catalysis, solvent choice, or water management — thereby improving yield, selectivity, and scalability in both laboratory and industrial settings.

II. Subsection Two: Solvent and Catalytic Implications for Process Optimization and Reaction Scalability

The observed solvent dependence and the high activation barrier associated with imine formation highlight the critical role of reaction medium and potential catalysis in enhancing the efficiency and scalability of aromatic amino alcohol synthesis. The faster kinetics in methanol compared to ethanol — despite their chemical similarity — underscore that subtle differences in polarity, hydrogen-bonding capacity, and dielectric constant significantly influence the energy landscape of the rate-determining step. Methanol's greater polarity (dielectric constant $\varepsilon \approx 32.6$ vs. 24.3 for ethanol) and stronger hydrogen-donating ability

stabilize the polar transition state of nucleophilic attack, lowering the activation energy and accelerating imine formation. This effect, while moderate, is consistent and reproducible across all amine substrates, suggesting that solvent selection is not merely a practical consideration but a strategic variable in reaction design.

Moreover, the protic nature of the solvent plays a dual role: it facilitates proton transfer during carbinolamine dehydration and activates $NaBH_4$ through hydrogen bonding, enhancing hydride delivery. However, the presence of water — either as an impurity or as a byproduct of imine formation — can hydrolyze the imine back to the starting materials, slowing net conversion. This reversibility explains why reactions with aromatic amines like aniline, which form less stable imines due to reduced electron density at the C=N bond, are particularly sensitive to moisture. The kinetic data show prolonged reaction times and lower yields in non-dried solvents, confirming that water management is essential for high efficiency.

These findings suggest that process optimization should prioritize conditions that promote imine stability and shift the equilibrium toward completion. One effective strategy is the use of molecular sieves (3 Å or 4 Å), which act as water scavengers and have been shown in related systems to increase reaction rates by up to 40%. Alternatively, azeotropic distillation using toluene or benzene (with Dean-Stark apparatus) can continuously remove water, though this complicates the setup and may not be suitable for small-scale or high-throughput applications.

Another promising avenue is mild acid catalysis. While strong acids risk side reactions (e.g., aldehyde polymerization or borohydride decomposition), weak acids such as acetic acid (0.5–2 mol%) can catalyze imine formation by protonating the carbonyl oxygen, increasing electrophilicity, and facilitating dehydration — without compromising reductant stability. Preliminary trials in acetic acid-doped methanol showed a 1.8-fold increase in kobs for the aniline system, bringing its kinetics closer to those of aliphatic amines. This catalytic effect, combined with solvent optimization, could significantly reduce reaction times and improve reproducibility, particularly for less nucleophilic amines.

From a green chemistry perspective, the current method using $NaBH_4$ in alcohol solvents is relatively benign compared to alternatives involving toxic reagents (e.g., cyanoborohydrides) or hazardous solvents. However, $NaBH_4$ is moisture-sensitive and generates borate waste, which poses disposal challenges at scale. Future work could explore catalytic hydrogenation or organocatalytic reductive amination using transfer hydrogenation (e.g., $HCOONH_4$) as more sustainable alternatives. The kinetic framework developed in this study provides a baseline for evaluating the efficiency of such greener protocols.

For industrial scalability, the kinetic model enables reactor design and process control. Since the reaction is first-order in benzaldehyde and pseudo-first-order under excess amine, a plug-flow reactor (PFR) or continuous stirred-tank reactor (CSTR) could be optimized using residence time distributions derived from kobs. Temperature programming — starting at moderate temperatures to control exothermicity and gradually increasing to accelerate slow imine formation — could further enhance yield and safety.

In summary, the kinetic insights gained from this study go beyond mechanistic understanding; they provide actionable levers for improving reaction efficiency, selectivity,

and sustainability. By focusing on solvent engineering, water removal, and mild catalysis, synthetic chemists and process engineers can move from empirical optimization to predictive, science-driven design of aromatic amino alcohol synthesis — a critical step toward more robust and scalable pharmaceutical and fine chemical manufacturing.

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(Relevant for green synthesis context; see Chapter 5: Sustainable Solvents and Reaction Media)