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The role of micellar catalysis from kinetic and thermodynamic investigations of the reaction between bromhexine drug with *para*-dimethylaminobenzaldehyde

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Abstract

Kinetic study of the condensation reaction of bromhexine with *para*-dimethylaminobenzaldehyde (DAB) in weakly acidic EthOH/H_2O has been investigated. An opposite first order reaction with respect to bromhexine and zero order with respect to DAB has been observed. The rate constants, activation energies, frequency factors, and other related thermodynamic functions of activation for both forward and reverse reactions have been determined. Standard thermodynamic parameters including equilibrium constant, ΔG°, ΔH°, and ΔS° have been calculated. The effect of the presence of anionic surfactant (sodium dodecyl sulfate, SDS) upon these kinetic and thermodynamic parameters of this reaction in aqueous solution has been examined. The results indicate that the presence of 4×10^{-3} M SDS increase the forward and reverse rate constants together with equilibrium constant by 104.3, 19.48, and 5.33 times, respectively. A substantial increase in the values of frequency factors of 1×10^5 and 2×10^4 for forward and reverse reactions, respectively, due to the presence of this amount of SDS has been detected. The observed positive sign of ΔS° in presence and absence of SDS has been confirmed through conductivity measurements. The rate constants in micellar phase, binding constants between each bromhexine and DAB with SDS, and the change in standard chemical potential have been determined at different temperatures. Activation energy, frequency factor, and other related thermodynamic functions of activation in micellar phase have also been calculated. It has been concluded that the increases in the number of collisions between reactants molecules caused by presence of micelles plays a major role in the physicochemical properties of surfactants solutions.

Keywords: Micellar catalysis; Kinetic; Thermodynamic; Sodium dodecyl sulfate; Bromhexine; *Para*-dimethylaminobenzaldehyde

1. Introduction

Bromhexine hydrochloride (I) is used as expectorant in pharmaceutical preparations [1]. It seems to us interesting to investigate the effect of micelles upon the reaction of such biologically active material. This due to the fact that many biochemical processes proceed in microheterogeneous systems containing aqueous and lioplilic moiety [2–4].

Recently, the effect of the presence of anionic surfactant (sodium dodecyl sulfate SDS) upon the kinetic of condensation reactions of six sulphonamides [5] and three β-lactams [6] drugs with *p*-dimethylaminobenzaldehyde (DAB) was studied extensively. A substantial difference in kinetic behavior between those groups of drugs was observed, i.e. a relatively fast reaction of zero order with respect to sulphonamides and slow reversible reaction with first order with respect to β-lactams were found. The reason for this was mainly attributed to the position of amino group which subject to steric and resonance effects. In addition, the substituent of each group exhibit affects upon their kinetics behaviors. For example, the presence of SDS changes the sequence of rate constants for the substituents of both sulphonomides and β-lactams [5,6]. Such phenomenon was attributed to the molecular interactions between their polar and non-polar groups with surfactant or micelles. In general the addition of SDS increases the rate constants of these bimolecular reactions. However, the presence of bromine group in bromhexine attracted us to investigate its reactivity towards the presence of surfactant and to compare it with previous studied drugs.

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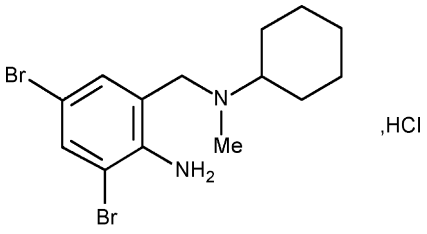


(I)

In the present work, kinetic and thermodynamic investigations of the reaction of bromhexine with DAB were explored in the absence and presence of SDS. Indeed, no such studies were mentioned in the literature.

2. Methods and materials

Bromhexine hydrochloride was obtained in highly pure form from State Drug Industry (SDI), Samarra-Iraq. All other reagents were analytical grade commercial products purified when necessary by standard procedures. Distilled water was used for preparation of all solutions; except these for conductivity measurements. The latter were prepared using conductivity water with specific conductance of 4–5 μS.

All spectral and kinetic measurements were performed on UV–vis Spectrophotometer Centra 5 (GBC Scientific Equipment) equipped with thermostated cell holder. Conductivity measurements were carried out on conductometer Consort C832 with accuracy of 0.01 μS. To control the temperature within ±0.1 °C, a water thermostated Hakke NK22 was used.

The stoke solutions were freshly prepared 0.009 and 0.001 M solutions of bromhexine hydrochloride for kinetic and conductometric measurements, respectively. 0.1 and 0.02 M solutions of DAB were prepared in ethanol (99.99%) and in 0.05 M SDS, respectively. 0.1 M solution of SDS was also prepared.

Kinetic measurements were normally used solutions of 1.5×10^{-3} and 5×10^{-5} M of bromhexine in absence and presence of SDS, respectively, with varying concentration of DAB. The former solution contained 0.087 M of KCl to avoid the effect of ionic strength and also for buffering composition (with desired amount of HCl) of the solution. No need to add KCl in the presence of SDS due to its negative effect to SDS and also the latter could do the same job for buffering composition [6]. Details of the experimental procedure were illustrated in ref. [5]. The observed rate constants were calculated with integral equations from the experimentally obtained profiles absorbance versus time. The calculations were performed with a computer using Microsoft Excel program for linear regression analysis. Multiple linear regression analysis was used for determining the binding constants using Minitab 11 software.

Conductivity measurements were carried out through placing 25 ml of conductivity water in the thermostated conductivity cell. 0.5 ml of 1×10^{-3} M bromhexine was injected into the cell then mechanically mixed and followed by measuring the conductivity of solution. More details about the procedure of this experiment were explained in ref. [7].

The Schiff base was prepared by reaction of 5×10^{-4} mol of bromhexine with stochiometric amount of DAB. Each reactant was dissolved in the minimum amount of ethanol followed by addition of 5 ml ethanol to the mixed solution. The latter was refluxed for 48 h and left for 24 h. The solid product was collected by filtration. The product was redissolved in ethanol for recrystallization to give a pale yellow product of mp equal to 242.7–245.6 °C.

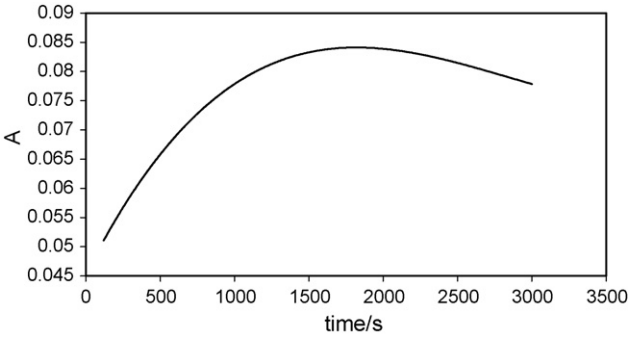


Fig. 1. Shows schematically the maximum in the relation between absorbance (λ = 425 nm) and time for the produced Schiff base from the reaction of 2×10^{-3} M of each bromhexine and DAB at pH 2 and 20 °C.

3. Results and discussions

The reaction of bromhexine with DAB in presence of HCl gives yellow colored solution due to the formed Schiff base, with an absorbance maximum at 425 nm [8]. Kinetic study was performed by following the increase of absorption intensity of the visible peak with time. A maximum was observed when one follows the relation between absorption versus time (Fig. 1). This indicates that the presented reaction is opposite or not completely forward. Such phenomenon was confirmed through the linearity of this relation [6]:

$$\frac{[\text{bromhexine}]}{A_{\text{eq}}} = \frac{1}{\varepsilon_{\text{Sb}}[\text{DAB}]K} + \frac{1}{\varepsilon_{\text{Sb}}} \quad (1)$$

where [bromhexine] and [DAB] are the concentration of drug and DAB, respectively. A_{eq} and ε_{Sb} are the absorbance at infinite time and extinction coefficient of the Schiff base, respectively. K is the concentration equilibrium constant of the reaction.

However, if the plot of [bromhexine]/A_{eq} versus 1/[DAB] gives a linear line, the reaction is reversible. A linear line with correlation coefficient equal to 0.991 was found as clearly illustrated in Fig. 2. It should be noted that Eq. (1) was derived through rearrangement of the following published relation [6,9]:

$$A_{\text{eq}} = \frac{\varepsilon_{\text{Sb}} K[\text{bromhexine}]_t[\text{DAB}]_t}{1 + K[\text{DAB}]_t} \quad (2)$$

The order of the presented reaction was explored through the following processes. The reaction of equal concentrations of both bromhexine and DAB gives a first order reaction when kinetic data where applied to first and second order rate equations (Table 1). The obtained first order reaction was confirmed using isolation method (Table 2). The results indicate that the reaction is first order with respect to bromhexine and zero order with respect to DAB. Such order of reaction was also found for the reaction of sulphonomides [5]. This may be attributed to the

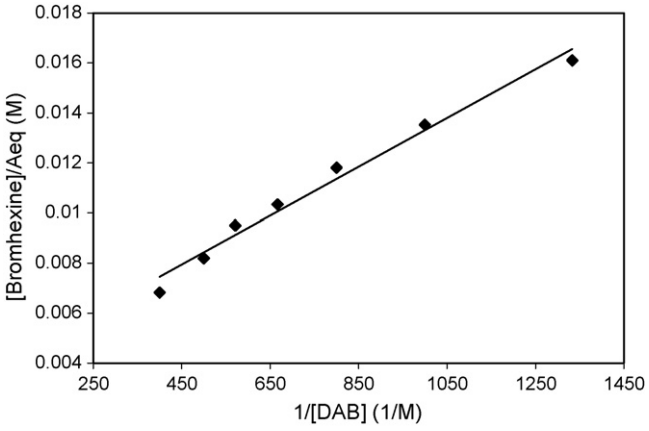


Fig. 2. The relation between [bromhexine]/A_{eq} and 1/DAB according to Eq. (1) for the reaction of 1.5×10^{-3} M bromhexine with various concentrations of DAB at pH 2 and 20 °C.

Table 1
Observed rate constants (k_r), order of reaction (n), square correlation coefficient (r^2), and standard error (S.E.) of the reaction between equal concentrations (2×10^{-3} M) of both reactants in the absence of SDS at pH 2 and 20 °C

Order	k_r	Intercept	r^2	S.E.
First	$0.002238\,s^{-1}$	−3.31	0.999	0.014
Second	$0.1229371\,mol^{-1}\,s^{-1}$	19.745	0.975	3.266

presence of aromatic amino group in contrast to that of β-lactams antibiotics [6].

The rate constants of Tables 1 and 2 were followed through expressing the initial concentration (a) by ($A_{eq} - A_o$) and the residual ($a - x$) by ($A_{eq} - A_t$) in the integrated rate equations of non-reversible reactions. Where A_{eq}, A_o, and A_t represent the absorbance at equilibrium (infinite time), zero time and time, respectively. Although, our reaction is reversible, therefore, the only difference in the expression of these terms is the rate constant (k) that would be equal to the sum of the forward and reverse reactions. This due to that the symbols (x_e) and ($x_e - x$) would be represented also by ($A_{eq} - A_o$) and ($A_{eq} - A_t$) according to the following equation:

$$\ln(x_e - x) = \ln x_e - (k_1 + k_{-1})t \quad (3)$$

where x_e and x represent the concentrations at equilibrium and time, respectively, k_1 and k_{-1} the forward and reverse rate constants, respectively, and t is the time.

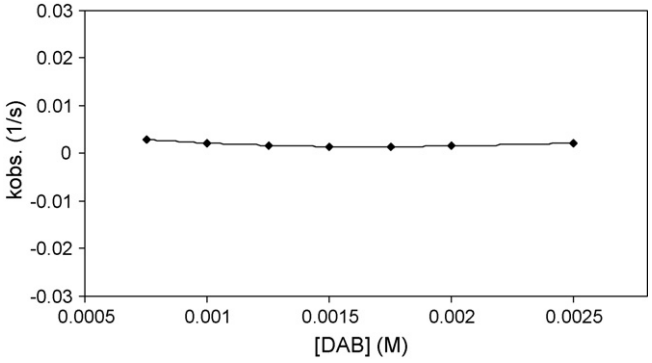


Fig. 3. The effect of DAB concentration upon the observed rate constant of 1.5×10^{-3} M bromhexine at pH 2 and 20 °C s^{-1}.

In general the proposed mechanism of this reaction may be expressed by following equation:

$$\text{Protonated[DAB]} + \text{Bromhexine} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\text{Intermediate}] \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \text{Schiff base} + H_2O \quad (4)$$

while the measured or observed rate constant could be represented by:

$$k_{(\text{observed})} = \frac{k_1 k_2}{k_{-1} k_{-2}} \quad (5)$$

It is apparent that the reverse reaction can also be first order due the relatively high concentration of H_2O whose representing the main solvent.

The effect of DAB concentration upon the observed rate constant was investigated and the results are illustrated in Fig. 3. The latter shows that there is no significant influence of DAB upon the observed rate constant through changing its concentration. This could also give confirmation to the order of the presented reaction which is first order with respect to bromhexine.

The effect of pH upon this reaction was also studied. Figs. 4–8 show the effect of pH on observed, forward, reverse rate constants, equilibrium constant and infinite absorbance, respectively. The relation of both observed and forward rate constants with pH exhibit somewhat similar shape with maxima (Figs. 4 and 5). The maximum of Fig. 5 indicates the predominance of forward reaction in contrast to the reverse which increases with increasing pH (Fig. 7). These phenomena may indicate that the increase in HCl concentration may stabilize the amino group and decrease its tendency towards attack by aldehyde group. On the other hand, the increase of pH may also leads to increase the rate of reaction through decreasing the con-

Table 2
Results of an application of isolation method for the presented reaction in the absence of SDS at pH 2 and 20 °C

[Bromhexine] (M)	[DAB] (M)	Order	k_r	Intercept	r^2	S.E.
5.2×10^{-4}	5.6×10^{-2}	Zero	$9.64 \times 10^{-5}\,mol\,l^{-1}\,s^{-1}$	0.02	0.934	0.002
5.2×10^{-4}	5.6×10^{-2}	First	$0.0097\,s^{-1}$	−3.145	0.997	0.028
7.5×10^{-3}[a]	1.5×10^{-4}	Zero	$4.07 \times 10^{-4}\,mol\,l^{-1}\,s^{-1}$	0.004	0.998	0.0002
7.5×10^{-3}[a]	1.5×10^{-4}	First	$0.064\,s^{-1}$	−4.256	0.98	0.069

[a] Its quite difficult to prepare higher than this concentration of bromhexine due to its limited solubility.

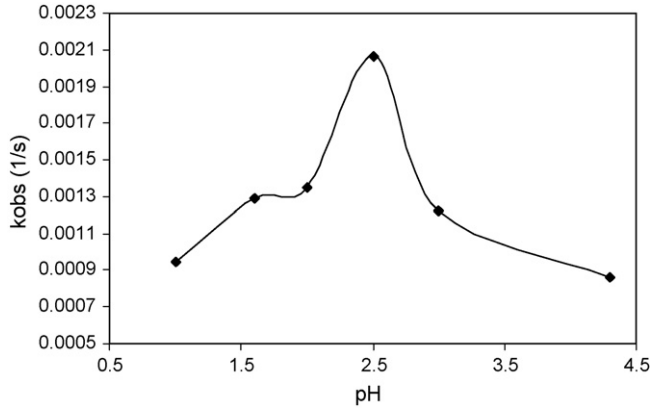


Fig. 4. Observed rate constant ($k_1 + k_{-1}$) of 1×10^{-3} M bromhexine and DAB vs. pH at 20 °C.

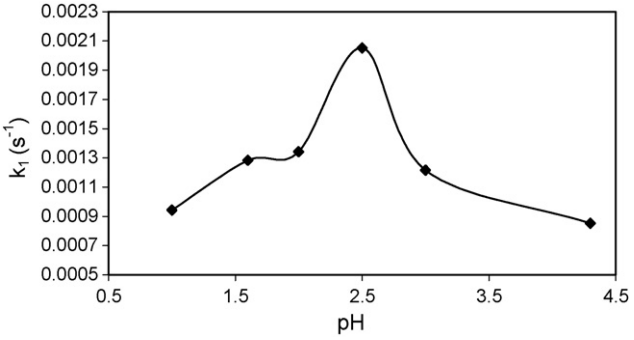


Fig. 5. Forward rate constant (k_1) of 1×10^{-3} M bromhexine and DAB vs. pH at 20 °C.

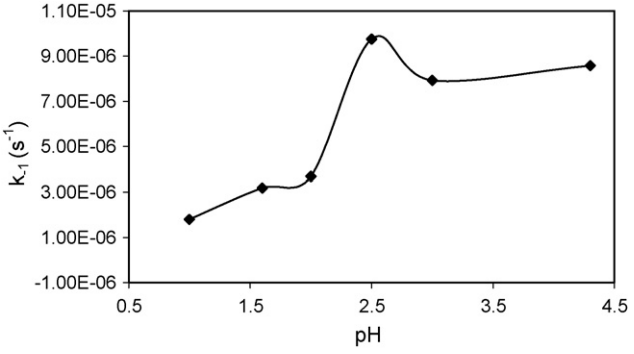


Fig. 6. Reverse rate constant (k_{-1}) of 1×10^{-3} M bromhexine and DAB vs. pH at 20 °C.

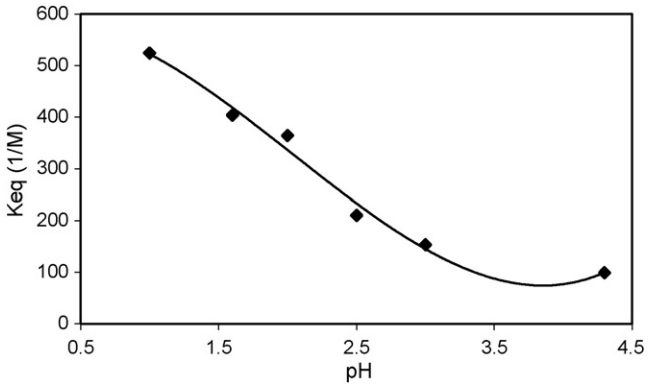


Fig. 7. Equilibrium constant (K_{eq}) of 1×10^{-3} M bromhexine and DAB vs. pH at 20 °C.

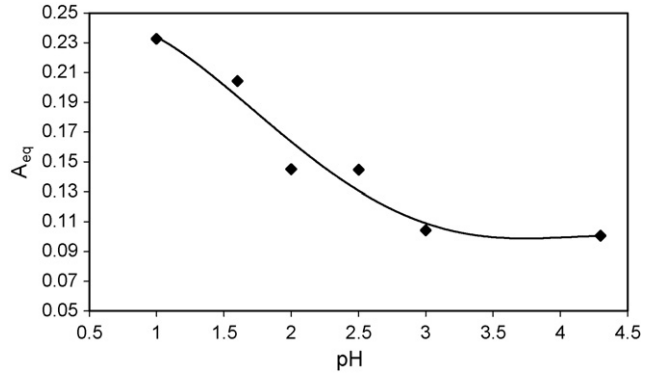


Fig. 8. Infinite absorbance (A_∞) of 1×10^{-3} M bromhexine and DAB vs. pH at 20 °C.

centration of protonated DAB and also through hydrolyzing the produced Schiff base. The decrease of infinite absorbance with increasing pH (Fig. 8) may be attributed to the deprotonation of imine nitrogen that is responsible for the coloring phenomenon of the Schiff base.

The effect of temperature upon the above parameters of this reaction was investigated and summarized in Table 3. The activation energies, frequency factors and other related thermodynamic functions of activation for the forward and reverse reactions were also determined and reported in Table 4. Both values of activation energies are over 20 kJ mol^{-1} indicating that those reactions do not depend on the diffusion rate [10]. The results also show there is a substantial difference between the values of frequency factors of forward and reverse reaction. The low value of the latter may be attributed to the cage effect

Table 3
Observed rate constants (k_{obs}), square of correlation coefficients (r^2), equilibrium constants (K_{eq}) forward (k_1) and reverse (k_{-1}) rate constants at different temperatures (pH 2)

T (°C)	k_{obs} (s^{-1})	r^2	K_{eq} (M^{-1})	r^2	k_1 (s^{-1})	k_{-1} (s^{-1})
10	7.64×10^{-4}	0.993	260.827	0.989	7.61×10^{-4}	2.92×10^{-6}
15	8.14×10^{-4}	0.995	349.197	0.994	8.11×10^{-4}	2.32×10^{-6}
20	1.35×10^{-3}	0.988	364.041	0.982	1.34×10^{-3}	3.69×10^{-6}
25	1.41×10^{-3}	0.999	433.834	0.98	1.41×10^{-3}	3.25×10^{-6}
30	3.62×10^{-3}	0.994	465.444	0.982	3.61×10^{-3}	7.75×10^{-6}

Table 4
Activation energies ($E^{\neq}$) frequency factors (A_1), free energy of activation ($\Delta G^{\neq}$), enthalpy of activation ($\Delta H^{\neq}$), entropy of activation ($\Delta S^{\neq}$) and equilibrium constants of activation ($K^{\neq}$) for the forward and reverse reactions of bromhexine with DAB

Reaction	$E^{\neq}$ (kJ mol^{-1})	A (s^{-1})	$\Delta G^{\neq}$ (kJ mol^{-1})	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J mol^{-1} K^{-1})	$K^{\neq}$
k_1	52	2.49×10^6	89.3	49.52	−133.4	2.27×10^{-16}
k_{-1}	32.3	2.08	104.35	29.82	−249.97	5.23×10^{-19}

Table 5
Standard thermodynamic functions for the reaction of bromhexine with DAB at pH 2 and 25 °C

ΔG° (kJ mol^{-1})[a]	ΔH° (kJ mol^{-1})[b]	ΔS° (J mol^{-1} K^{-1})[c]
−15.05	19.7	116.56

[a] Calculated from the relation $\Delta G^{\circ} = -RT \ln K_{eq}$.
[b] Determined from the slope of plot of $\ln K_{eq}$ (Table 3) vs. $1/T$ ($\ln K_{eq} = C - (\Delta H^{\circ}/RT)$) with $r^2 = 0.936$.
[c] Calculated from the relation $\Delta G^{\circ} = \Delta H^{\circ} - T\Delta S^{\circ}$.

which is caused by water molecules as solvent [10]. The difference between the equilibrium of activation for forward and reverse reactions is quite consistent with the resulted value of equilibrium constant (K_{eq}) (Table 3). However, it is apparent from the results of Table 4 that the reaction is predominated by the frequency factor or the number of collisions between reactants molecules rather than the activation energy.

The standard thermodynamic functions for the presented reaction were also determined and illustrated in Table 5. The positive value of ΔS° may be attributed to the homo-association of bromhexine and also to the electrostriction phenomenon that arises from reactants charged molecules.

The effect of the presence of SDS on the above kinetic and thermodynamic parameters was investigated. In this case, an aqueous solution of SDS was used for dissolving DAB instead of ethanol. A red shift in the maximum wavelength of the produced Schiff base from 425 to 430 nm was detected. Indeed, no shift caused by the presence of SDS was observed for the reactions of sulphonomides and β-lactams [5,6].

The order of the presented reaction was also investigated in the presence of SDS. No any effect was detected on the order of this reaction [11].

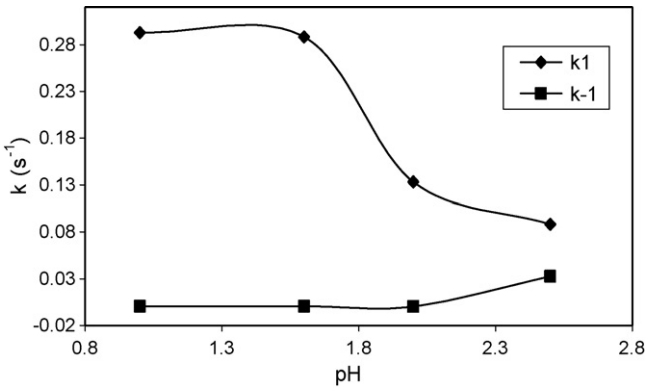


Fig. 10. Forward and reverse rate constants vs. pH for the reaction of 5×10^{-5} M bromhexine with 5×10^{-4} M DAB in presence of 0.00225 M SDS at 20 °C.

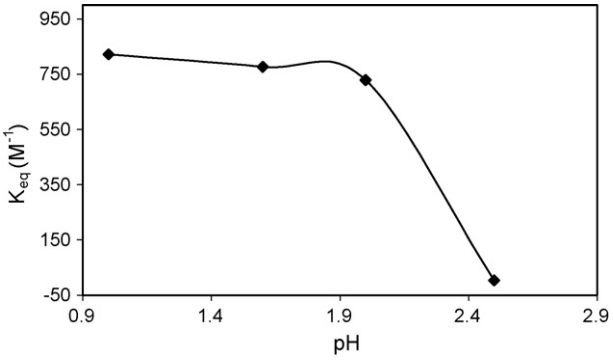


Fig. 11. Equilibrium constant vs. pH for the reaction of 5×10^{-5} M bromhexine with 5×10^{-4} M DAB in presence of 0.00225 M SDS at 20 °C.

Figs. 9–12 illustrate the effect of pH upon the observed rate constant ($k_1 + k_2$), forward and reverse rate constants, equilibrium constant, and infinite absorbance, respectively. The relationship between equilibrium constant and pH (Fig. 11)

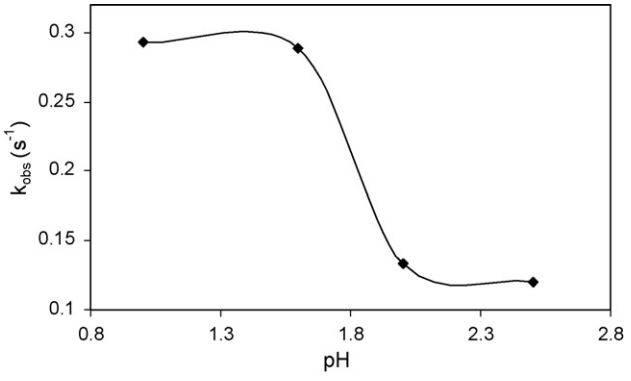


Fig. 9. Observed rate constant vs. pH for the reaction of 5×10^{-5} M bromhexine with 5×10^{-4} M DAB in presence of 0.00225 M SDS at 20 °C.

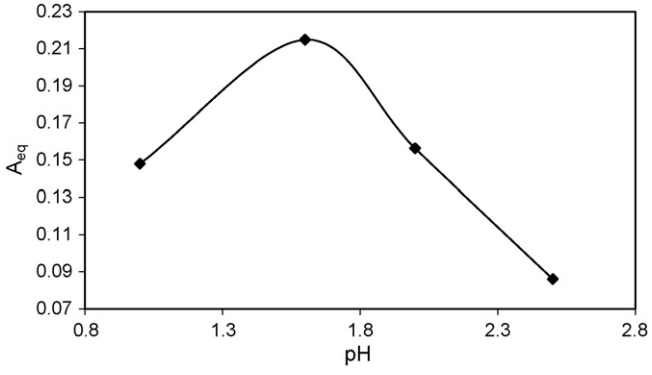


Fig. 12. Infinite absorbance vs. pH for the reaction of 5×10^{-5} M bromhexine with 5×10^{-4} M DAB in presence of 0.00225 M SDS at 20 °C.

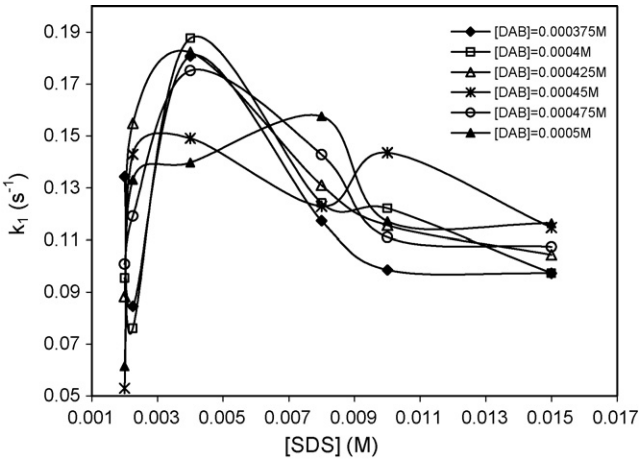


Fig. 13. Effect of [SDS] upon the forward rate constant for the reaction between 5×10^{-5} M bromhexine with different concentrations of DAB at pH 2 and 20 °C.

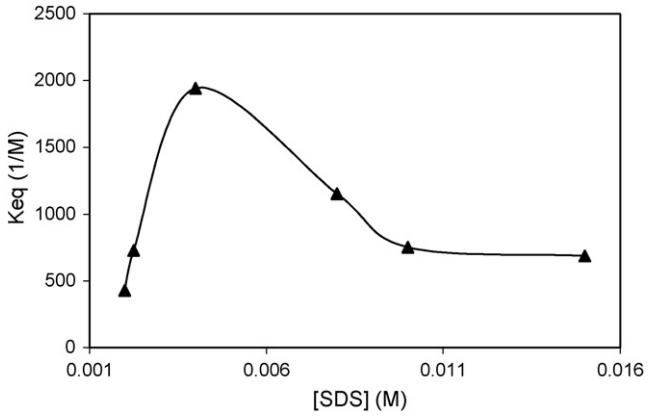


Fig. 15. Effect of [SDS] upon the equilibrium constant for the reaction between 5×10^{-5} M bromhexine with different concentrations of DAB at pH 2 and 20 °C.

is consistent with the values of critical micelle concentration (cmc). The latter possesses values of 0.001, 0.00225, 0.00407, and 0.0074 M at pH equal to 1, 2, 3, and 7, respectively [12,13]. This could also explain the relation for observed and forward rate constants with pH as they are shown in Figs. 9 and 10, respectively. The relation of Fig. 12 may be interpreted by the same reasons of the above mentioned for Fig. 8.

Figs. 13–16 explain the effect of SDS upon the forward and reverse rate constants, equilibrium constants, and infinite absorbance at different concentrations of DAB, respectively. The maxima of Fig. 13 are used for bimolecular reactions which attributed to the effect of concentration and dilution of reactants molecules by micelles [14]. In contrast, the relation for reverse rate constant in the presence of [SDS] exhibits a minimum (Fig. 14). This may be explained by that the micelles cores are occupied by Schiff base molecules, and when the micelles species are increased a dilution of Schiff base could take place in the cores which may give them more chance to react with water molecules. The maxima of Figs. 15 and 16 might be attributed to the relatively ideal concentration of SDS that could gives a best yield of the product with respect to bromhexine concentration.

Table 6 listed the effect of temperature upon observed, forward and reverse rate constants, together with the equilibrium constant at different concentrations of SDS. It was found that both forward and reverse rate constants are obeyed to Arrhenius equation. The activation energies, frequency factors, and other related thermodynamic functions of activation for forward and reverse reactions are reported in Tables 7 and 8, respectively.

The standard thermodynamic functions were also determined at different concentrations of SDS (Table 9). The ΔG° values showed a maximum at 0.004 M SDS. This may be explained by that at this specific concentration of SDS the orientations and interactions of the product molecules give more stability than that in other concentrations of SDS.

Table 10 summarized a whole comparison between the calculated parameters in absence and presence of 0.004 M SDS. It should be noted that the presence of SDS leads to substantial increase in the rate of reaction; therefore, the kinetic measurements in the presence of SDS were followed in lower initial concentrations.

However, the equilibrium constant was increased five times due to the presence of SDS. While, the activation energies for both forward and reverse reactions are somewhat increased in the

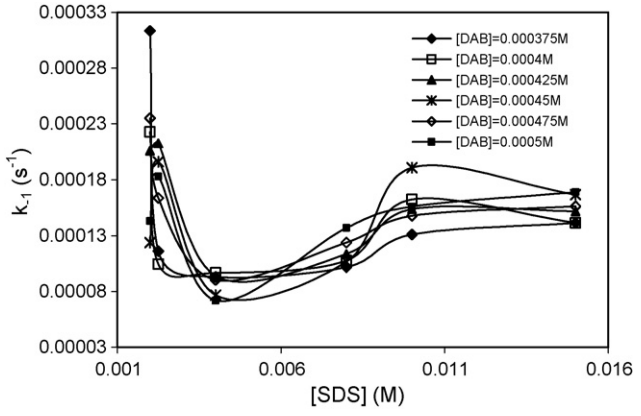


Fig. 14. Effect of [SDS] upon the reverse rate constant for the reaction between 5×10^{-5} M bromhexine with different concentrations of DAB at pH 2 and 20 °C.

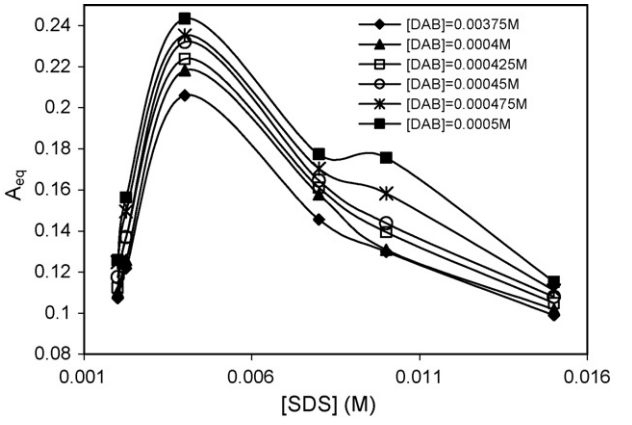


Fig. 16. Effect of [SDS] upon the infinite absorbance for the reaction between 5×10^{-5} M bromhexine with different concentrations of DAB at pH 2 and 20 °C.

Table 6
Observed, forward and reverse rate constants together with the equilibrium constant of the reaction of 5×10^{-5} M bromhexine with 5×10^{-4} M DAB in presence of different amounts of SDS at different temperatures and pH 2

T (°C)	[SDS] (M)	k_{obs} (s^{-1})	K_{eq} (M^{-1})	k_1 (s^{-1})	k_{-1} (s^{-1})
10	0.00175	0.12413	1.65×10^{-3}	2.05×10^{-4}	1.24×10^{-1}
	0.002	0.119	54.04	0.1168	2.16×10^{-3}
	0.00225	0.0786	357.09	0.0784	2.2×10^{-4}
	0.004	0.0918	1625.84	0.0917	5.64×10^{-5}
	0.008	0.0698	759.87	0.0697	9.18×10^{-5}
	0.01	0.0695	602.68	0.0693	1.15×10^{-4}
	0.015	0.0536	551.57	0.0535	9.7×10^{-5}
15	0.00175	0.0973	2.51×10^{-3}	2.44×10^{-4}	9.70×10^{-2}
	0.002	0.112	298.65	0.1116	3.74×10^{-4}
	0.00225	0.1052	506.78	0.1050	2.07×10^{-4}
	0.004	0.123	1880.63	0.1229	6.54×10^{-5}
	0.008	0.0971	834.89	0.0970	1.16×10^{-4}
	0.01	0.0851	682.63	0.0850	1.25×10^{-4}
	0.015	0.0876	628.43	0.0875	1.39×10^{-4}
20	0.002	0.0616	428.63	0.0614	1.43×10^{-4}
	0.00225	0.1333	728.43	0.1331	1.83×10^{-4}
	0.004	0.1398	1942.87	0.1398	7.19×10^{-5}
	0.008	0.1577	1153.88	0.1575	1.37×10^{-4}
	0.01	0.1173	752.17	0.1171	1.56×10^{-4}
	0.015	0.1165	688.17	0.1163	1.69×10^{-4}
25	0.002	0.1555	435.1	0.1551	3.57×10^{-4}
	0.00225	0.2563	798.58	0.2560	3.21×10^{-4}
	0.004	0.2279	2027.66	0.2278	1.12×10^{-4}
	0.008	0.1909	1302.35	0.1908	1.47×10^{-4}
	0.01	0.2255	989.57	0.2253	2.28×10^{-4}
	0.015	0.1182	753.77	0.1181	1.57×10^{-4}
30	0.002	0.3369	521.84	0.3363	6.44×10^{-4}
	0.00225	0.4191	947.43	0.4187	4.42×10^{-4}
	0.004	0.7471	3124.81	0.7468	2.39×10^{-4}
	0.008	0.2022	2304.7	0.2021	8.77×10^{-4}
	0.01	0.3372	1279.9	0.3396	2.63×10^{-4}
	0.015	0.2634	1077.35	0.2631	2.44×10^{-4}

Table 7
Activation energy, frequency factor, and thermodynamic functions of activation for the forward reaction of bromhexine and DAB in presence of different amounts of SDS at 25 °C and pH 2

[SDS] (M)	$E_1^{\neq}$ (kJ mol^{-1})	A_1 (s^{-1})	$\Delta G_1^{\neq}$ (kJ mol^{-1})	$\Delta H_1^{\neq}$ (kJ mol^{-1})	$\Delta S_1^{\neq}$ (J mol^{-1} K^{-1})	$\Delta H_1^{\neq}$ (M^{-1})
0.002	34.59	2.37×10^5	77.65	32.11	−152.73	2.5×10^{-14}
0.00225	60.34	9.36×10^9	76.4	57.86	−62.19	4.12×10^{-14}
0.004	68.15	2.72×10^{11}	76.69	65.67	−36.98	3.67×10^{-14}
0.008	49.26	8.55×10^7	77.13	46.78	−101.81	3.07×10^{-14}
0.01	58.85	4.33×10^9	76.72	56.37	−68.24	3.63×10^{-14}
0.015	49.66	7.93×10^7	78.32	47.18	−104.44	1.9×10^{-14}

Table 8
Activation energy, frequency factor, and thermodynamic functions of activation for the reverse reaction of bromhexine and DAB in presence of different amounts of SDS at 25 °C and pH 2

[SDS] (M)	$E_{-1}^{\neq}$ (kJ mol^{-1})	A_{-1} (s^{-1})	$\Delta G_{-1}^{\neq}$ (kJ mol^{-1})	$\Delta H_{-1}^{\neq}$ (kJ mol^{-1})	$\Delta S_{-1}^{\neq}$ (J mol^{-1} K^{-1})	$K_{-1}^{\neq}$ (M^{-1})
0.002	36.22	837.86	92.71	33.74	−197.78	5.74×10^{-17}
0.00225	40.94	4.64×10^3	92.97	38.46	−182.84	5.16×10^{-17}
0.004	48.57	4.26×10^4	95.57	46.09	−165.96	1.81×10^{-17}
0.008	22.04	1.11	94.91	46.78	−252.72	2.36×10^{-17}
0.01	32.17	91.14	93.82	19.56	−215.09	3.66×10^{-17}
0.015	28.07	15.55	94.75	29.67	−231.95	2.52×10^{-17}

Table 9
Standard thermodynamic functions at different concentrations of SDS for the reaction of bromhexine and DAB at pH 2 and 25 °C

[SDS] (M)	ΔG° (kJ mol^{-1})	ΔH° (kJ mol^{-1})	ΔS° (J mol^{-1} K^{-1})
0.002	−15.06	24.63	133.1
0.00225	−16.57	34.49	171.25
0.004	−18.88	19.58	128.99
0.008	−17.78	27.22	150.91
0.01	−17.1	26.69	146.85
0.015	−16.42	21.6	127.51

presence of SDS. This phenomenon indicates that the catalytical action of micelles does not involve the reduction of activation energy as the normal catalyst does. In other word, the collision parameter is the predominate factor as clearly shown from the values of frequency factors for the forward and reverse reactions in the absence and presence of SDS (Table 10). Although, the increase of activation energy, $\Delta G^{\neq}$, and $\Delta H^{\neq}$ in the presence of SDS might be attributed to the increase in the potential energy which resulted from molecular interactions due to the closeness of molecules within the core of micelle. The increases of potential energy could also be resulted from the attraction forces. The latter arises from the positively charged hemiaminal intermediate with the negative charges of anionic micelle. Such attraction could also stabilize the intermediate and then become a secondary factor for increasing the rate of reaction. The increases of $\Delta S^{\neq}$ value due to the presence of SDS for forward and reverse reactions may be related to dependency of this parameter on the number of collisions or frequency factor. The equilibrium constants of activation for forward and reverse

Table 10
Summarizes the difference in calculated parameters of the presented reaction in absence and presence of SDS

The parameter	Reaction in the absence of SDS	Reaction in the presence of 0.004 M SDS
[Bromhexine] (M)	0.001	0.00005
[DAB] (M)	0.001	0.0005
λ_{max} (nm)	425	430
k_1 (s^{-1}) at (20 °C)	1.34×10^{-3}	0.1398
k_{-1} (s^{-1}) at (20 °C)	3.69×10^{-6}	7.19×10^{-5}
K_{eq} (M^{-1}) at (20 °C)	364.04	1942.87
$E_1^{\neq}$ (kJ mol^{-1})	52	68.15
$E_{-1}^{\neq}$ (kJ mol^{-1})	32.3	48.57
A_1 (s^{-1})	2.49×10^{6}	2.72×10^{11}
A_{-1} (s^{-1})	2.08	4.26×10^{4}
$\Delta G_1^{\neq}$ (kJ mol^{-1})	89.3	76.69
$\Delta G_{-1}^{\neq}$ (kJ mol^{-1})	104.35	95.57
$\Delta H_1^{\neq}$ (kJ mol^{-1-})	49.52	65.67
$\Delta H_{-1}^{\neq}$ (kJ mol^{-1})	29.82	46.09
$\Delta S_1^{\neq}$ (J mol^{-1} K^{-1})	−133.4	−36.98
$\Delta S_{-1}^{\neq}$ (J mol^{-1} K^{-1})	−249.97	−165.96
$K_1^{\neq}$ (M^{-1})	2.27×10^{-16}	3.67×10^{-14}
$K_{-1}^{\neq}$ (M^{-1})	5.23×10^{-19}	1.81×10^{-17}
ΔG° (kJ mol^{-1})	−15.05	−18.88
ΔH° (kJ mol^{-1})	19.7	19.58
ΔS° (J mol^{-1} K^{-1})	116.56	128.99

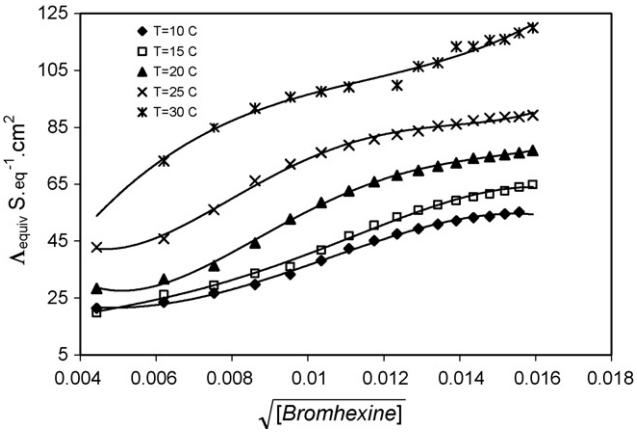


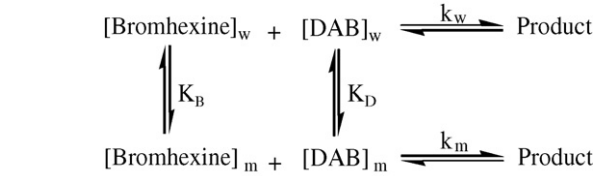
Fig. 17. Equivalent conductance vs. $\sqrt{[\text{Bromhexine}]}$ (application of Kohlraush equation) for aqueous solution of bromhexine at different temperatures.

reactions were increased by 160 and 35 times, respectively, due to the presence of SDS.

Indeed no significant effect upon the standard thermodynamic functions (ΔG°, ΔH° and ΔS°) due to the presence of SDS has been observed. The positive value of ΔS° whether in absence or presence of SDS attracted us to investigate the conductivity behavior of the solution of bromhexine. The results of the treatment of conductimetric data for bromhexine in aqueous solution using Kohlraush equation [7] at different temperatures indicate the presence of accumulated bromhexine ions. The latter was realized from the increases in equivalent conductance with increasing the square root of bromhexine concentration as clearly shown in Fig. 17. This could definitely give the reason for the positive sign of standard entropy (ΔS°).

The above kinetic data were employed to calculate the binding constants of bromhexine (K_B) and DAB (K_D) with SDS together with the rate constant in micelle phase (k_m) at different temperatures (Table 11). The latter parameters were determined using multiple linear regression method that illustrated briefly in ref. [6]. The change in the standard chemical potential of the bromhexine ($\Delta\mu_B^\circ$) and DAB ($\Delta\mu_D^\circ$) on passing from water to micellar were also calculated and listed in Table 11. The value of rate constant in micelle (k_m) increases as usual with increasing temperature. These values of rate constants suggest that the reaction is not captured by micellar phase but also occurs in water phase according to the following scheme (Scheme 1), where k_w is the rate constant in water.

The results (Table 11) show that the binding constant of bromhexine with SDS is higher that of DAB. This may be attributed to the binding of both hydrophobic and hydrophilic



where k_w is the rate constant in water.

Scheme 1.

Table 11
Rate constant in micellar phase, binding constants and transfer free energies at different temperatures

T (°C)	k_m (s^{-1})	K_B (M^{-1})	K_D (M^{-1})	$-\Delta\mu_B^\circ$ (kJ mol^{-1})	$-\Delta\mu_D^\circ$ (kJ mol^{-1})
10	7.19×10^{-4}	2668.28	53.70	28.03	18.83
15	1.15×10^{-3}	1589.34	52.16	27.28	19.1
20	1.5×10^{-3}	731.11	63.24	25.86	19.9
25	1.61×10^{-3}	[a]	[a]	[a]	[a]
30	2.77×10^{-3}	[a]	[a]	[a]	[a]

[a] Cannot determine due to poor correlation which resulted from the enhanced rate of reaction at those temperatures.

Table 12
Activation energy, frequency factor and other related thermodynamic functions of activation in micellar phase

$E_m^{\neq}$ (kJ mol^{-1})	A_m (s^{-1})	$\Delta G_m^{\neq}$ (kJ mol^{-1})	$\Delta H_m^{\neq}$ (kJ mol^{-1})	$\Delta S_m^{\neq}$ (J mol^{-1} K^{-1})	$K_m^{\neq}$
43.329	7.46×10^4	73.021	40.85	−107.9	1.61×10^{-13}

groups of bromhexine with micelle compared to only hydrophobic binding of DAB. In addition, the hydrophobic part of the latter is quite smaller than that of bromhexine. The apparent decreases in binding constant of bromhexine with increasing temperature could be attributed to the decrease in molecular associations. The somewhat increase in the binding constant of DAB with micelles at 20 °C might be attributed to the competitive binding with bromhexine as the binding of the latter decreased significantly at this temperature.

The values of the change in the standard chemical potential suggest that the bromhexine possesses more penetrated inside the core of micelle than DAB.

The values of rate constants at different temperature in micellar phase (Table 11) were treated by Arrhenius equation to calculate the activation energy, frequency factor and other related thermodynamic functions of activation in micellar phase (Table 12). No such treatment for this kind of data was observed in the literature. It was found that there is a consistency of k_m with Arrhenius equation which give r^2 equal to 0.946. The relatively low values of $E_m^{\neq}$ and A_m in contrast to the above observed for forward and reverse reactions also indicate that the reaction not only occurs in micellar phase. The closeness of $\Delta G_m^{\neq}$ value to those for forward and reverse reactions may indicate that the reaction is mostly occurs in micellar phase.

It should be noted that some of the above results were employed for microdetermination of bromhexine in aqueous solution of SDS and applied successfully to its pharmaceutical preparations [14].

4. Conclusions

On the basis of our results one could generally conclude that the principle of micellar catalysis completely differs from that of normal homogeneous catalyst for the following reasons:

(1) The catalytical action of micelles does not involve the reduction of activation energy through changing the mechanism of the reaction.
(2) The increase in rate of reaction caused by the presence of micelle is due to the increase in the number of collisions between reactants molecules and to stabilize the intermediate by the opposite charge of anionic surfactant.
(3) The latter point could also give the reason for increasing the equilibrium constant by micelles. While, normal catalyst should not affect this parameter.
(4) The catalyst may involve or take part in the reaction, but the micelle does not.
(5) The rate of reaction increased by increasing the concentration of catalyst, while for micelle there is a maximum.

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