Kinetic and Thermodynamic Investigations of the Reaction between Metoclopramide Hydrochloride and para-Dimethylaminobenzaldehyde

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Abstract

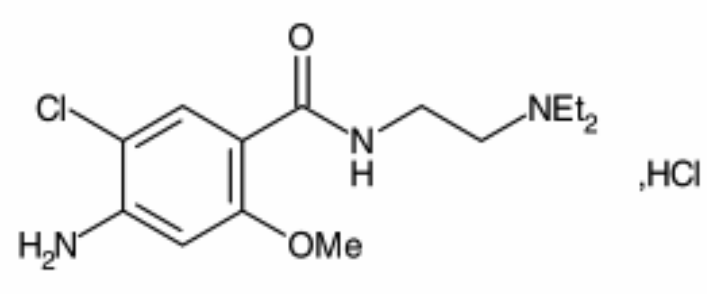
Kinetic study of the condensation reaction of metoclopramide drug with para-dimethylaminobenzaldehyde (DAB) in weakly acidic EtOH/H_2O has been investigated. A reversible first order reaction with respect to DAB and zero order with respect to metoclopramide has been observed. The rate constants, activation energies, pre-exponential factors, and other related thermodynamic functions of activation for both forward and reverse reactions have been determined. Standard thermodynamic parameters including equilibrium constant, ΔG^o, ΔH^o, and ΔS^o have been calculated.

الخلاصة

تضمن البحث دراسة حركية ثرموداينميكية لتفاعل عقار ميتوكلوبراميد مع بارا- ثنائي مثيل بنزالديهايد في وسط حامضي ومذيب الماء/الكحول. واثبتت الدراسة أن التفاعل عكسي من الرتبة الأولى بالإعتماد على تركيـز البنزالديهايد ومن الرتبة صفر باللإعتماد على تركيز الدواء. كما تم إيجاد ثابت السرعة، طاقة التنشيط، معامل ما قبل الأس وباقي القيم الثرموداينميكية للتنشيط للتفاعلين الأمامي والعكسي. كذلك تم حساب القيم الثرموداينميكيـة القياسية للتفاعل التي شملت ثابت التوازن، الطاقة الحرة لجبس، الإنثالبي والإنتروبي.

Introduction

Metoclopramide hydrochloride (I) is one of psychopharmacological agents [1], it is used as antiemetic in pharmaceutical preparations [2]. It seems to us interesting to investigate the formation of Schiff base because of importance of such materials. Their derivatives have a remarkable biological activity. They are used as anticancer [3], Antibacterial [4], Antifungal and Antiviral [5]. Recently, kinetic of condensation reactions of six sulphonamides [6], bromhexine [7], three β-lactams [8] and benzocaine [9] drugs with p-dimethylaminobenzaldehyde (DAB) in the presence of surfactants 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, so as benzocaine, little fast reversible reaction of first order with respect to bromhexine 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.



(I)

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

Methods and materials

Metoclopramide hydrochloride was obtained in a 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. All spectral and kinetic measurements were performed on Shimadzo UV-160A Spectrophotometer with thermostated cell holder. To control the temperature within ±0.1 ^{o}C, a water thermostated Thermo Haake K20 was used. The stoke solutions were freshly prepared 0.05M solutions of metoclopramide hydrochloride for measurements. 0.025M solutions of

DAB were prepared in ethanol (99.99%). Kinetic measurements were normally used solutions of 2×10^{-3}M of metoclopramide with varying concentration of DAB. The former solution contained 0.087M of KCl to avoid the effect of ionic strength and also for buffering composition (with desired amount of HCl) of the solution [10]. Details of the experimental procedure were illustrated in ref. [6]. The observed rate constants were calculated with integral equations from the experimentally obtained profiles absorbance versus time. The calculations were performed by a computer using Microsoft Excel program for linear regression analysis.

Results and discussions

The reaction of metoclopramide and DAB in presence of HCl gives yellow colored solution due to the formed Schiff base, with an absorbance maximum at 446 nm (438 nm according to Patel et al. [11]. 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 [8]:

$$\frac{[Metoclopra\,mide]}{A_{eq}} = \frac{1}{\varepsilon_{Sb}[DAB]K} + \frac{1}{\varepsilon_{Sb}} \quad (1)$$

where [Metoclopramide] 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 [Metoclopramide]/A_{eq} versus 1/[DAB] gives a linear line, the reaction be reversible. A linear line with correlation coefficient equal to 0.999 was found as clearly illustrated in Fig. 2. It should be noted that Eq. (1) was derived through rearrangement of the following published relation [8,12]:

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

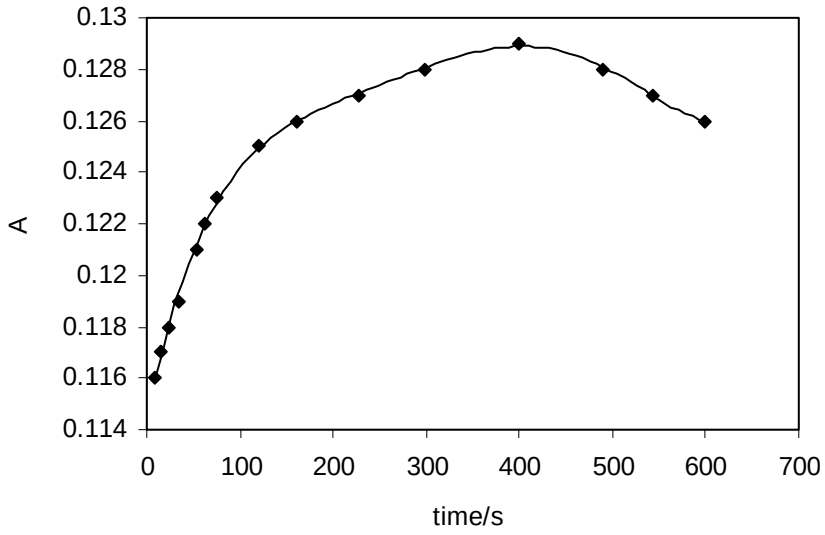


Fig. 1: The relation between absorbance (λ = 446 nm) and time for the produced Schiff base from the reaction of 2×10^{-3} M of each metoclopramide and DAB at pH 2 and 20°C.

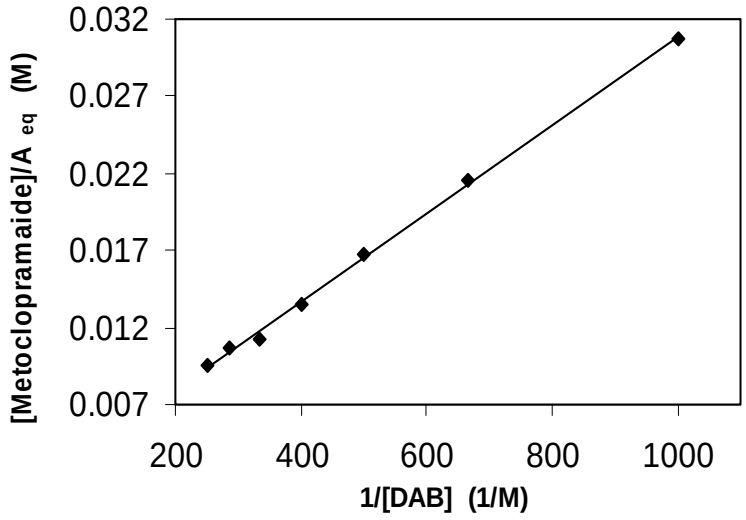


Fig. 2: The relation between [metoclopramide]/Aeq and 1/DAB according to Eq. (1) for the reaction of 2×10^{-3} M metoclopramide with various concentrations of DAB at pH 2 and 20°C.

According to this study and the previous, we have found that the reversible phenomenon depends significantly upon the chemical structure of amine. In other words the resonance effect plays a major role in the phenomenon of reversibility. For example the presence of two bromine groups in ortho- and para- position of the bromhexine amino group [7], and chlorine group in ortho- position of the

metoclopramide amino group leads to a remarkable opposite reaction. For sulphonamides [6] and benzocaine [9] the reaction is somewhat completely forward, due to the similarity in chemical structure. While the non-aromatic amine group of β-lactam antibiotics also leads to a reversible reacton [8].

The order of the presented reaction was explored through the following processes. The reaction of equal concentrations of both metoclopramide and DAB gives a first order reaction when kinetic data where applied to first and second order rate equations (Table1). As the values of r^2 closed together, first order reaction can be proved by standard error values. The obtained first order reaction was confirmed using isolation method (Table 2). The results indicate that the reaction is zero order with respect to metoclopramide and first order with respect to DAB. Such order of reaction was also found for the reaction of sulphonomides [6] and benzocaine [9]. 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:

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

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

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

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

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

It is obvious that the reverse reaction can also be first order due the relatively high concentration of H_2O which represents the main solvent. The effect of metoclopramide 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 metoclopramide.

The effect of pH upon this reaction was also studied. Table 3 and Figs. 4–8 show the effect of pH on observed, forward, reverse rate constants, equilibrium constant and infinite absorbance, respectively. No reaction can be observed at pH more than 3. 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. 6). 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 decrease the rate of reaction through decreasing the concentration 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 4. The activation energies, pre-exponential 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 [13]. The results also show that there is a substantial difference between the values of pre-exponential factors of forward and reverse reaction. The low value of the latter may be attributed to the cage effect which is caused by water molecules as solvent[13]. The difference between the equilibrium of activation for forward and reverse reactions is quite consistent with the resulted value of equilibrium constant (K_{eq}) at the same temperature (25^oC) (Table 4). The positive value of enthalpy of activation of forward reaction seems logical, because the reaction needs energy no less than activation energy to proceed. However, it is apparent from the results of Table 4 that the reaction is predominated by the pre-exponential factor or the number of collisions between reactants molecules rather than the activation energy. The positive value of $\Delta S^{\neq}$ of forward reaction may attributed to electrostriction phenomenon that arises from reactants charged molecules.

The standard thermodynamic functions for the presented reaction were also determined and illustrated in Table 5.

Table 1: Observed rate constants (kr), 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 at pH 2 and 20^oC

Order	k_r	Intercept	r^2	S.E.
First	0.4457 s^{-1}	-2.648	0.998	0.011
Second	10.688 $l.mol^{-1}.s^{-1}$	11.925	0.993	0.689

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

[Metoclopramide] (M)	[DAB] (M)	Order	k_r	Intercept	r^2	S.E.
1×10^{-3}	5×10^{-2}[a]	Zero	0.02338 $mol.l^{-1}.s^{-1}$	0.015	0.973	1.19×10^{-3}
1×10^{-3}	5×10^{-2}[a]	First	0.64801 s^{-1}	-2.989	0.96	4.03×10^{-2}
0.1	1×10^{-3}	Zero	0.17861 $mol.l^{-1}.s^{-1}$	1.764	0.765	0.137
0.1	1×10^{-3}	First	0.86606 s^{-1}	0.148	0.99	0.122

[a] Its quite difficult to observe the reaction with higher than this concentration of DAB.

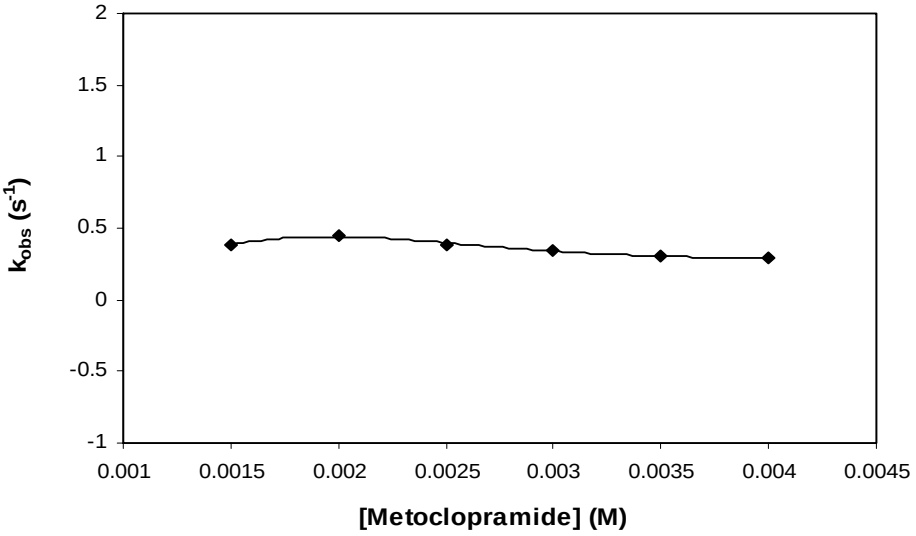


Fig. 3: The effect of metoclopramide concentration upon the observed rate constant of 2×10^{-3} M DAB at pH 2 and 20°C.

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 pH and 20°C.

pH	k_{obs} (s^{-1})	r^2	K_{eq} (M^{-1})	r^2	k_1 (s^{-1})	K_{-1} (s^{-1})
3	0.1583	0.991	15.395	0.981	0.1486	9.66×10^{-3}
2.5	0.4409	0.991	34.876	0.999	0.4287	1.23×10^{-2}
2	0.4457	0.998	78.361	0.998	0.4401	5.62×10^{-3}
1.6	0.7636	0.993	7.24	0.989	0.6709	9.27×10^{-2}
1	0.1479	0.988	2.445	0.999	0.105	4.29×10^{-2}

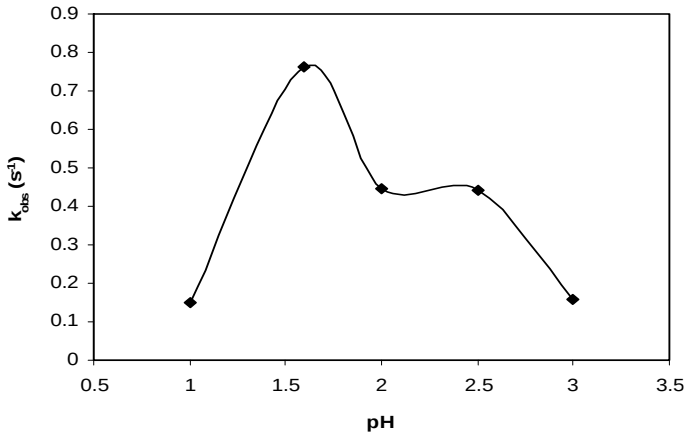


Fig. 4: Observed rate constant ($k_1 + k_{-1}$) of 2×10^{-3} M metoclopramide and DAB vs. pH at 20°C.

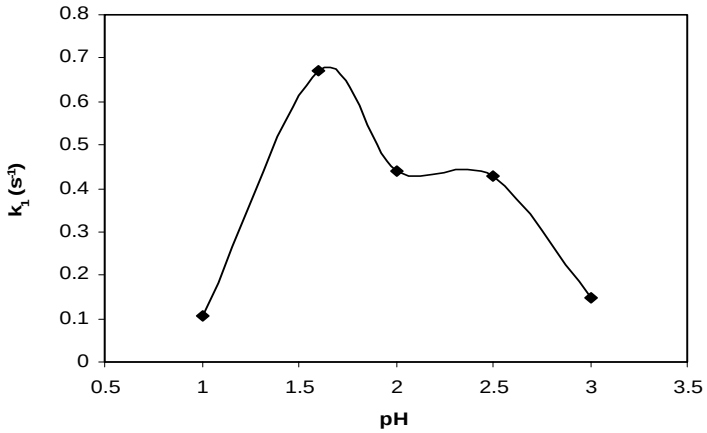


Fig. 5: Forward rate constant (k_1) of 2×10^{-3} M metoclopramide and DAB vs. pH at 20°C.

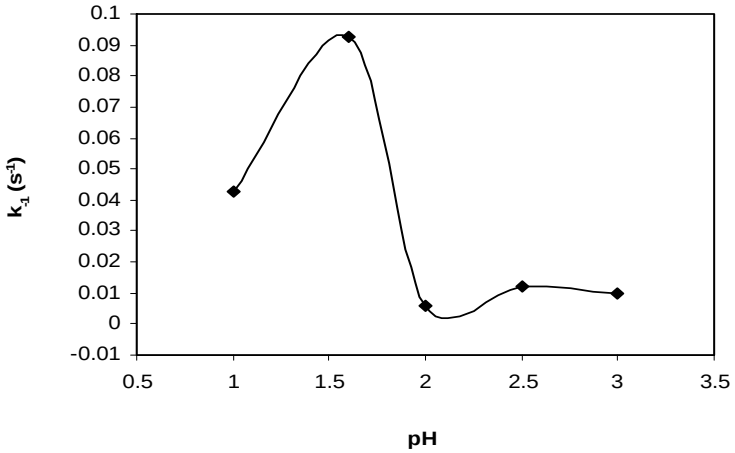


Fig. 6: Reverse rate constant (k_{-1}) of 2×10^{-3} M metoclopramide and DAB vs. pH at 20°C.

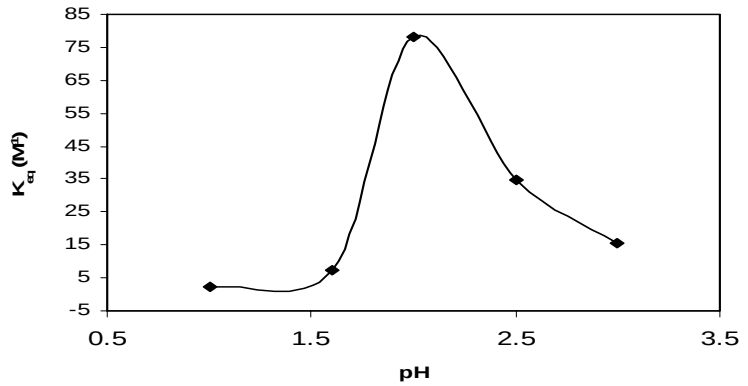


Fig. 7: Equilibrium constant (K_{eq}) of 2×10^{-3} M metoclopramide and DAB vs. pH at 20°C.

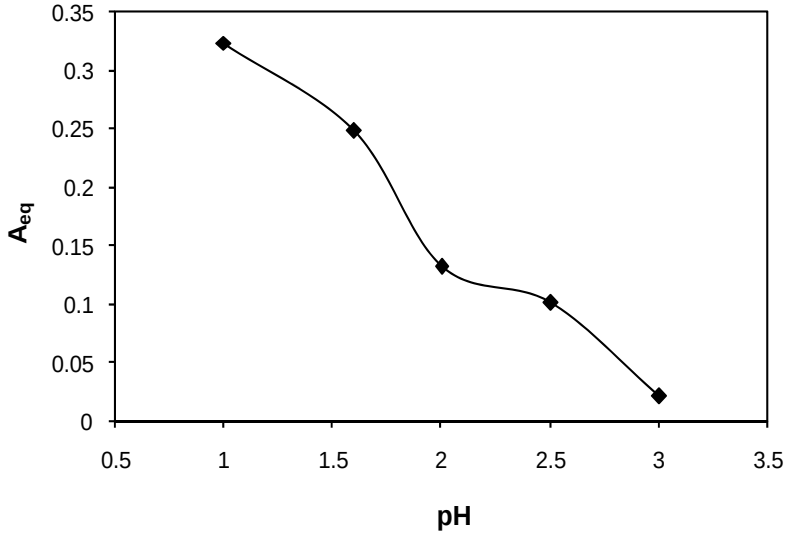


Fig. 8: Infinite absorbance (A_∞) of 2×10^{-3} M metoclopramide and DAB vs. pH at 20°C.

Table 4: 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})
6	0.0536	0.984	23.932	0.986	0.0515	2.15×10^{-3}
10	0.0545	0.999	32.46	0.997	0.0529	1.63×10^{-3}
15	0.1933	0.999	42.876	0.999	0.1889	4.41×10^{-3}
20	0.4457	0.998	78.361	0.998	0.4401	5.62×10^{-3}
25	1.1399	0.991	102.089	0.996	1.1288	1.12×10^{-2}

Table 5: Activation energies ($E^{\neq}$) pre-exponential 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 metoclopramide 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	120.155	$1.15x10^{21}$	72.72	117.68	150.77	$1.82x10^{-13}$
k_{-1}	65.6	$3.06x10^{9}$	84.19	63.12	-70.68	$1.78x10^{-15}$

Table 6: Standard thermodynamic functions for the reaction of metoclopramide with DAB at pH 2 and 25^{o}C.

ΔG^{o} (kJ.mol^{-1})[a]	ΔH^{o} (kJ.mol^{-1})[b]	ΔS^{o} (J.mol^{-1}.K^{-1})[c]
-11.47	54.56	144.53

a Calculated from the relation $\Delta G^{o} = -RT \ln K_{eq}$.

b Determined from the slope of plot of $\ln K_{eq}$ (Table 3) vs. 1/T

($\ln K_{eq} = C - (\Delta H^{o}/RT)$) with $r^2 = 0.983$

c Calculated from the relation $\Delta G^{o} = \Delta H^{o} - T\Delta S^{o}$

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