Correlation Analysis for the Kinetics Data of the Reaction between Some Sulphonamides with p- Dimethylaminobenzaldehyde[+]

دراسة التحليل الارتباطي للنتائج الحركيه لتفاعل بعض ادوية السلفا مع مركب بارا- ثنائي مثيل امينوبنزالديهايد

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Abstract:

The main objective of this paper was to establish the factors affecting the rate constant for the reaction of six sulpha drugs with p- dimethylaminobenzaldehyde (DAB) through correlation analysis. Four parameters belonging to the sulphonamides have been suggested. The first was taking the type of sulphonamide amino group (N) primary, secondary, or tertiary. The second was for steric effect (M) which takes the number of the bulky methyl group into account. The third was the molecular weight (m.wt) of the sulphonamide molecule. The last one was belonging only to metal effect (S) for the sulphonamide containing metal ion. The correlation analysis was applied to the reaction of sulphonamide in the absence and presence of anionic surfactant (Sodium dodecyl sulphate, SDS). The results show that the parameter M is the predominant one in absence of SDS, while in the presence of SDS; N parameter is the predominant one. Additive parameters for the rate constant of these reactions in the absence and presence of SDS have been suggested with good standard deviation.

المستخلص:

إن الهدف الرئيسي لهذا البحث هو تعيين العوامل المؤثرة على حركية التفاعل لستة من أدوية السلفا مع مركب بارا- ثنائي مثيل أمينوبنزالديهايد(DAB) من خلال طريقة التحليل الإرتباطي. لقد تم إقتراح أربع عوامل لهذه الدراسة، حيث يمثل العامل الأول نوع مجموعة الأمين العائدة للسلفوناميد إن كانت هذه المجموعة أحادية، ثنائية أو ثلاثية ويرمز لهذا العامل بـ N. أما العامل الثاني فيبحث في تأثير الإعاقة الفراغية والتي تمثل عدد مجاميع المثيل الموجودة في مركب السلفوناميد ويرمز له بـ M. العامل الثالث هو الوزن الجزيئي لمركب السلفوناميد و يرمز له بـ m.wt. أما العامل الأخير فيعود لتأثير وجود أيون فلزي في تركيب السلفوناميد ويرمز له بـ S. ولقد طبقت هذه التقنية على تفاعل السلفوناميد مع DAB بوجود وعدم وجود العامل الفعال سطحيا الأنيوني صوديوم دوديسيل سلفيت (SDS). وأظهرت النتائج أن العامل M هو المسيطر في حالة عدم وجود ألـSDS بينما يكون العامل N هو المسيطر في حالة وجود ألـSDS. وقد تم إقتراح معاملات إضافة لثابت السرع لهذه التفاعلات عند وجود وعدم وجود SDS مع قيم جيدة للإنحراف المعياري.

Introduction:

It is well known that the main objective of correlation analysis is to summarize and analyze the empirical results in order to reveal the fundamental factors belonging to these data [1]. Indeed, correlation analysis becomes a powerful tool for interpretation, predicting and

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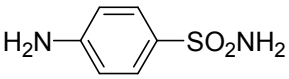
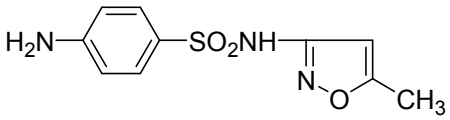
understanding the physical properties of systems. For example, correlation analysis for NMR chemical shifts were performed using multiple linear regression [2] and simultaneous linear equations method [3] to give additivity parameters having two significant advantages: The first for predicting chemical shift of unknown substituents, while, the second could aid in understanding the factors that influence the chemical shifts of the studied molecules.

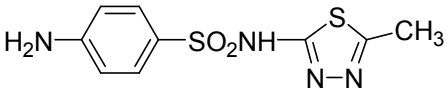
Recently, we were studied the effect of anionic surfactant (Sodium dodecyl sulphate, SDS) on kinetic of reaction of six sulpha drugs I-VI with p-dimethylaminobenzaldehyde(DAB) [4]. It was found that it is quite difficult to give any hint correlating the values of rate constants for these substances with their chemical structures in the absence and presence of SDS. Therefore, it seems to us interesting to investigate such data using correlation analysis. This might be useful for determining the main factors affecting the rate constants according to their chemical structures. It should be noted that the presented reaction between sulpha drugs with DAB produce Schiff bases. The latter compounds are considered as an important group of organic molecules. For example, some Schiff bases and their complexes with metals behave as antibiotics, antiviral and antitumor agent's [5]. Also, azomethine compounds have wide range of applications in many biological aspects, visual pigments, enzymic aldolization and decarboxylation reaction [6-8]. Recently, we have proved that the Schiff base produced from sulphanilamide with DAB can be used as an acid-base indicator [9].



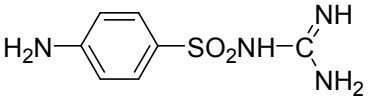
Sulfanilamide
(I)



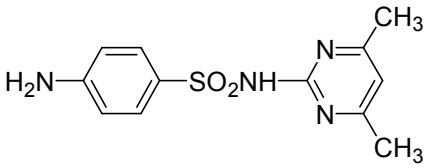
Sulfamethoxazole
(II)



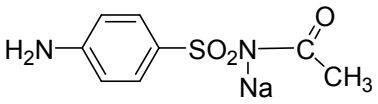
Sulfamethizole
(III)



Sulfaguanidine
(IV)



Sulfadimidine
(V)



Sulfacetamide sodium
(VI)

Experimental:

The first order rate constants of 0.5mM of sulphonamides I-VI and DAB in 20% Ethanol and in 0.5mM SDS at pH 2 and 20^{o}C have been taken from our previous research [4] and illustrated in Table 1. The work of multiple linear regression analysis has been carried out by PC computer using Minitab V. 11 software.

Table 1. Rate constants of 0.5 mM of sulphonamides I-VI with 0.5 mM of DAB in 20% ethanol and in 0.5 mM SDS at 20°C and pH=2 is taken from ref. 4.

Sulphonamide	$K_{in\ 20\%\ ethanol}$ (s^{-1})	$k_{in\ SDS}$ (s^{-1})
I	0.005758	0.2429665
II	0.005527	0.0172725
III	0.004606	0.0310905
IV	0.005067	0.0151998
V	0.0076	0.0347753
VI	0.00737	0.2040458

Result and Discussion:

Indeed, we are first who suggest to derive additivity parameters for treatment of kinetic data. This was for the reaction between some sulphonamides with HCl and iron II sulphate [10]. However, the suggested additivity parameters possessed some weak points from the chemical, physical, and statistical point of views. i.e. there was one parameter belonging to the presence of ring (in addition to the benzene ring) in the structure of sulphonamides which obviously cannot distinguished the apparent difference between these rings existing in II, III and V. Therefore, in this study we are trying to suggest additivity parameters for the presented reaction with no weak points and having advantage in illustrating the factors affecting the rate constant and also for predicting the rate constants of unknown sulphonamides with DAB in the absence and presence of SDS.

According to the structures of the studied sulpha drugs I-VI one could predicts the following parameters. The first parameter N represents the type of sulphonamide amino group; primary, secondary or tertiary. The coefficient of this parameter (α) which has the values 0, 1 and 2 for primary, secondary, and tertiary sulphonamide amino group respectively. The second parameter M may represents the steric effect that belonging to the presence of the bulky methyl group in the structure of sulphonamides. While β represents the coefficient of the latter parameter which its values represent the number of methyl group. i.e. for I, II and V β are equal to 0, 1 and 2 respectively. The third parameter m.wt represents the molecular weight of sulphonamides which may somewhat cover the additional groups in their structure. γ is the coefficient of m.wt parameter which its value equals to the molecular weight of the sulphonamide. The last parameter S represents the presence of metal that is especially for compound VI. δ is the coefficient of S parameter which have the value of 1 for compound VI and zero for others I-V. Thus, the above suggested parameters can be summarized by following equation.

$$k = C + \alpha N + \beta M + \gamma(m.wt) + \delta S \qquad (1)$$

Where k is the first order rate constant of the reaction between sulphonamides with DAB at 20°C, C is the constant term. For example, k for sulphanilamide I can be determined as follows:

1. The amino group that bonded directly to SO_2 has two hydrogen atoms, therefore, α =2.
2. There is no methyl group, therefore, β =0.
3. γ is belonging to the molecular weight of sulphanilamide and therefore will be equal to 172.20686.
4. There is no metal ion, therefore, δ =0.

Hence, equation 1 for this compound can be presented by equation 2.

$$k = C + 2N + 172.20686(m.wt) \qquad (2)$$

In order to determine the weight of each of suggested parameters, the treatment of the values of rate constants by these parameters will be separately at the first time. Then will take two parameters and so on, as illustrated in Table 2. The results show that when the parameters have been taken separately the M parameter is the predominant one with r^2 equal to 0.358. The reason for this may beyond to the steric effect caused by bulky methyl groups but also to the hydrophobic interactions between these groups of sulphonamide molecules. The molecular weight m.wt gives the lowest significance parameter with r^2 value equal to 0.088. However, the N, M and S parameters give a good r^2 with a value of 0.987 and therefore the equation for the presented reaction in the absence of SDS can be represented by

$$k = C + \alpha N + \beta M + \delta S \qquad (3)$$

The S parameter possesses the highest weight which may be related to the considerable solubility of the substrate resulted from the presence of metal. Table (3) listed the observed and calculated rate constant according to the equation 3 with difference between them (Δ). A good standard deviation with a value of 4.236×10^{-4} s^{-1} has been found indicating the success of our proposed parameters. However, the presence of m.wt parameter improve the r^2 square and standard deviation but not very significant in constant to other parameters.

Table 2. Regression analysis results for the kinetic data of sulphonamides I-VI with DAB in 20% ethanol at 20°C and pH=2.

Parameter	Constant term	Value of parameter			r^2	S. E.
N	0.000679	-0.000806			0.173	0.001248
M	0.00517	0.000975			0.358	0.0011
m.wt	0.00381	0.000009			0.088	0.001311
S	0.00571	0.00166			0.304	0.001145
N, M	0.00568	N 0.000387	M 0.000839		0.391	0.001237
N, m.wt	0.000639	N -0.00075	m.wt 0.000001		0.174	0.00144
N, S	0.00564	N 0.00006	S 0.00173		0.305	0.001321
M, m.wt	0.0113	M 0.0024	m.wt 0.00003		0.586	0.00102
M, S	0.005	M 0.000888	S 0.00148		0.598	0.001005
m.wt , S	0.00419	m.wt 0.000006	S 0.00155		0.347	0.001281
N, M, m.wt	0.0204	N -0.00176	M 0.00335	m.wt -0.000064	0.987	0.000222
N, m.wt , S	-0.00175	N 0.00186	m.wt 0.000022	S 0.00352	0.461	0.001424
m.wt , S, M	0.0123	m.wt -0.000036	S 0.00174	M 0.00256	0.911	0.00058
N, S, M	0.00311	N 0.00132	S 0.00299	M 0.00127	0.731	0.001007

Table 3. Observed and calculated rate constants according to eq.1 with Δ(Δ= $k_{observed} - k_{calculated}$) of sulphonamides I-VI with DAB in 20% ethanol at 20°C and pH=2.

Sulphonamide	$k_{observed}$ (s^{-1})	$k_{calculated}$ (s^{-1})	Δ
I	0.005758	0.00575	0.000008
II	0.005527	0.0057	-0.000173
III	0.004606	0.0057	-0.001094
IV	0.005067	0.00443	0.000637
V	0.0076	0.00697	0.00063
VI	0.00737	0.00737	0.0
Standard Deviation	----	----	4.236×10^{-4}

It is apparent that only one of the presented drugs possesses a metal ion VI. Therefore, we have tried to investigate the presented work with excluding this compound from the presented treatment (Table 4). In other word, the S parameter will be excluded. The results of Table 4 also show that M parameter is the predominant one and m.wt parameter is the less significant one. The best values of r^2 are 0.871 and 0.987 which may be represented by equation 4 and 5 respectively.

$$k = C + \beta(m.wt) + \gamma M \qquad (4)$$

$$k = C + \alpha N + \beta(m.wt) + \gamma M \qquad (5)$$

Table 4. Regression analysis results for the kinetic data of sulphonamides I-V with DAB in 20% ethanol at 20°C and pH=2.

Parameter	Constant term	Value of parameter			r^2	S. E.
N		0.00006			0.001	0.001321
M		0.000888			0.422	0.001005
m.wt		0.000006			0.060	0.001281
N, M		N	M		0.613	0.001007
		0.00132	0.00127			
N, m.wt		N	m.wt		0.226	0.001424
		0.00186	0.000022			
M, m.wt		M	m.wt		0.871	0.0005805
		0.00256	-0.000036			
N, m.wt ,M	0.0225	N	m.wt	M	0.987	0.0002628
		-0.00222	0.000071	0.00355		

The observed and calculated rate constants together with the Δ values according to the equation 4 and 5 are listed in Table 5. The results exhibit that the standard deviation of equation 4 (only two parameters) is better than that of equation 3. However, the addition of N parameter to those in equation 4 (as presented in equation 5) only improves the standard deviation by 4 factors.

Table 5. Observed and calculated rate constants according to eqs.4 and 5 with Δ of sulphonamides I-V with DAB in 20% ethanol at 20°C and pH=2.

Sulphonamide	$k_{observed}$ s^{-1}	$k_{calculated}$ by eq. 4	Δ	$k_{calculated}$ by eq. 5	Δ
I	0.005758	0.006101	-0.000343	0.005833	-0.000075
II	0.005527	0.005742	-0.000215	0.005847	-0.00032
III	0.004606	0.005128	-0.000522	0.004636	-0.00003
IV	0.005067	0.004587	0.00048	0.005068	-0.000001
V	0.0076	0.0074	0.0002	0.007618	-0.000018
Standard Deviation	----	----	3.52×10^{-4}	----	8.88×10^{-5}

Table 6 illustrated the effect of the presence of SDS upon the presented investigations. There is an apparent change in the predominance of the suggested parameters due to the presence of SDS which take the following consequence m.wt > S> M> N. While, in the absence of SDS the following consequence was noticed: M> S> N> m.wt (Table 2). In general, the presence of SDS shows clear improvement in the correlation coefficients. According to the values of r^2, three equations (6, 3 and 7) could represent the additivity parameters of the presented reaction in presence of SDS.

$$k = C + \alpha N + \delta S \qquad (6)$$

$$k = C + \alpha N + \beta(m.wt) + \delta S \qquad (7)$$

Applications of the above equations (6, 3 and 7) are illustrated in Table 7. The results indicate that equation 6 is not acceptable due to the relatively large standard deviation ($0.03573 s^{-1}$). Equation 3 also gives the best fit to the data which is parallel to that in the absence of SDS. The value of standard deviation of equation 3 in the presence of SDS can be considered better than that in the absence of the latter due to the substantial increasing in the rate constants caused by the presence of SDS.

Table 6. Regression analysis results for the kinetic data of sulphonamides I-VI DAB in 5.0mM SDS at 20°C and pH=2.

Parameter	Constant Term	Value of Parameter		r^2	S. E.
N	0.0714	0.0195		0.014	0.1152
m.wt	0.441	-0.00146		0.317	0.09588
S	0.0683	0.0136		0.286	0.09803
M	0.13	-0.0468		0.115	0.1091
N, m.wt	0.681	N -0.0694	m.wt -0.00217	0.42	0.102
N, S	-0.194	N 0.218	S 0.398	0.995	0.009793
N, M	0.136	N -0.0048	M -0.0484	0.116	0.1259
m.wt , S	0.482	m.wt -0.00174	S 0.1655	0.724	0.07034
m.wt , M	0.730	m.wt -0.00298	M 0.092	0.420	0.0102
S, M	0.113	S 0.147	M -0.0554	0.445	0.009974
N, m.wt , S	-0.295	N m.wt 0.243 0.00030	S 0.422	0.999	0.00582
N, m.wt , M	1.33	N m.wt -0.116 -0.00521	M 0.155	0.665	0.09496
m.wt , S, M	0.823	m.wt S -0.00354 0.173	M 0.109	0.866	0.06008
N, S, M	-0.213	N S 0.228 0.408	M 0.00979	0.998	0.006932

Table7. Observed and calculated rate constants according to eqs. 6, 3 and 7 with Δ of sulphonamides I-VI with DAB in SDS 0.5mM at 20°C and pH=2.

Sulphonamide	$k_{obs.}$ s^{-1}	$k_{cal.}$ by eq. 6	Δ	$k_{cal.}$ by eq. 3	Δ	$k_{cal.}$ by eq. 7	Δ
I	0.242967	0.242	0.000967	0.243	-0.000033	0.242662	0.000305
II	0.017273	0.024	-0.006727	0.02479	-0.007517	0.023985	-0.006712
III	0.031091	0.024	0.007091	0.02479	0.006301	0.0291	0.001991
IV	0.015200	0.024	-0.0088	0.015	0.0002	0.012274	0.002926
V	0.034775	0.024	0.010775	0.03458	0.000195	0.031501	0.003274
VI	0.204046	0.204	0.180046	0.20479	-0.000744	0.203273	0.000773
Standard Deviation	----	----	0.03573	----	2.4983×10^{-3}	----	2.6635×10^{-3}

Table 8 listed the effect of excluding the parameter belonging to the presence of metal ion (VI). A remarkable difference in the predominance with that of Table 4 in the absence of SDS was also found. i.e. an excellent correlation with N parameter (r^2 =0.993) according to equation 8 has been found.

$$k = C + \alpha N \qquad (8)$$

This gives prove that correlation analysis is not confident and depends on probability factor. In other words, the results are adjusted in such a way to give the best correlation coefficient and standard error. Therefore, a considerable precaution should be taken for such treatments [11].

Table 8. Regression analysis results for the kinetic data of sulphonamides I-V with DAB in 0.5mM SDS at 20°C and pH=2.

Parameter	ınstant Term	Value of Parameter			r^2	S. E.
N	-0.194	0.218			0.993	0.009793
m.wt	0.482	-0.00174			0.614	0.07034
M	0.113	-0.0554			0.224	0.09974
		N	m.wt			
N, m.wt	-0.295	0.243	0.0003		0.998	0.005820
		N	M			
N, M	-0.213	0.228	0.00979		0.997	0.006932
		m.wt	M			
m.wt , M	0.823	-0.00354	0.109		0.812	0.06008
		N	m.wt	M		
N, m.wt , M	-0.287	0.242	0.000273	0.001	0.998	0.008210

Equations 9 and 10 give good fit as indicated in Table 8. The calculated rate constants according to equations 8, 9 and 10 with their difference values from the observed have been shown in Table 9. The standard deviations according to equations 9 and 10 are close to each other indicating that the type of amino group that bonded directly to SO_2 play a major role in the presence of SDS. However, we prefer equation 9 in comparison to that of 10 due to the fact that there is no two substrates having same value of rate constant in contrast to these II and III of equation 10. The reason for the significance of N parameter in presence of SDS may be attributed to the homo and hetero association through hydrogen bond by amino group. Even tertiary amino group could makes hydrogen bond with other hydrogen atom. The hetero associations could occur through the polar hydrogen of ethanol as a co-solvent.

$$k = C + \alpha N + \beta(m.wt) \qquad (9)$$

$$k = C + \alpha N + \gamma M \qquad (10)$$

Table 9. Observed and calculated rate constants according to eq. 8, 9 and 10 with Δ of sulphonamides I-V with DAB in SDS 0.5mM at 20°C and pH=2.

phonamide	k_{obs} s^{-1}	k_{cal} by eq. 8	Δ	$_{cal}$ by eq. 9	Δ	eq. 10	Δ
I	0.242967	0.242	0.000967	0.242662	.000305	43	.000033
II	0.017273	0.024	-0.00673	0.023985	.00671	2479	0.00752
III	0.031091	0.024	0.007091	0.0291	001991	2479	.006301
IV	0.015200	0.024	-0.0088	0.012274	002926	015	0.0002
V	0.034775	0.024	0.010775	0.031501	003275	3458	.000195
Standard Deviation	----	----	$.8726\times 10^{-3}$	----	41×10^{-3}	---	$.85\times10^{-3}$

Conclusions:

In general, we could conclude that the presented equations could play a good role in estimating the rate constants of unknown substrates with a considerable physical meaning. The prediction term can be realized from the low values of Δ according to equations 1,5,3 and 10 as presented in tables 3,5,7 and 9 respectively. While the latter term of physical meaning could be explained by that the N and M parameters are the predominant factors affecting the rate constant of the condensation reaction between sulpha drugs with DAB in the absence and presence of SDS. The M parameter is related to the steric hindrance and to the hydrophobic interaction which could cause the icebergs structure [12] between water molecules and then affect the rate of reaction in the absence of SDS. While in presence of SDS such effect may be eliminated due to the interaction between the latter molecules and methyl group. The N parameter is related to weak molecular interactions through hydrogen bond with respect to the type of amine.

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