.Development of a New Set of Additive Parameters Affecting the Rate of Substitution of Bromoalkylamine

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Abstract

The effects of different substituents and ring size of reacting molecules on the rate constant for a substitution reaction of a set of fifteen bromoalkylamine have been studied. The geometries for all compounds under study were optimized at Hartree- Fock (HF) level with (3-21G) bases sets using chemoffice (version 11) suite of programs.

The charge with bond length and angle at the reaction centre coupled with strain energy for the reacting molecules was correlated with experimental values of the rate constant for substitution reaction. The results show that the charge at the carbon atom is the most important factor for the series of reactions of the same number of carbon atom while strain energy is the most significant factor when the number of carbon atom is changed in the series.

Key Words: Additive parameters, Rate of substitution, Bromoalkyl amine.

Introduction

The influence of a substituent plays a fundamental role on the observed physical and chemical properties of compounds. For example, the substituent effects influence the rates of nucleophilic substitution reaction[1] which contribute to differences in thermal properties[2], nuclear magnetic resonance chemical shifts[3] and positions of UV absorption bands [4]. In general, the substituent alters the reactivity, conformation and related properties of the material . The most common studies of substituent effects have focused on the influence of the substitution on a single molecular property [5]. More recently the applicability of quantum chemical parameters as descriptors for substituent effects on the pk'$_a$ s of substituted benzoic acid[6],anilines and phenols[7] was studied. The aim of the present work is to examine the applicability of quantum chemical parameters as descriptors for substituent effects on the rate of substitution reactions of bromoalkylamines.

Methods

The geometries of 15 cycloalkylamine were optimized using abinitio calculations performed with GAMESS software, at the restricted Hartree- Fock level, using the standard 3-21G basis set[8]. These geometries were then used to compute the charge on the two carbon atom, bond length and angles coupled with the total strain energy which compute by using molecular mechanic theory 2 (MM2). The experimental value of rate constants was taken from ref.9.

Results and Discussions

The replacement of bromide group by thiosulphate ion in some bromoalkylamine ($Br-(CH_2)_n-NH_2$) has been studied kinetically in a basic medium at pH equal to 8.9 . It has been found that reaction proceeds via the formation of a cyclic intermediate resulting from intramolecular substitution of bromide group by the amino group leading to a cyclic intermediate . After the formation of the cyclic intermediate the reaction proceeds by the addition of thiosulphate ion leading to the product, as shown in scheme I.

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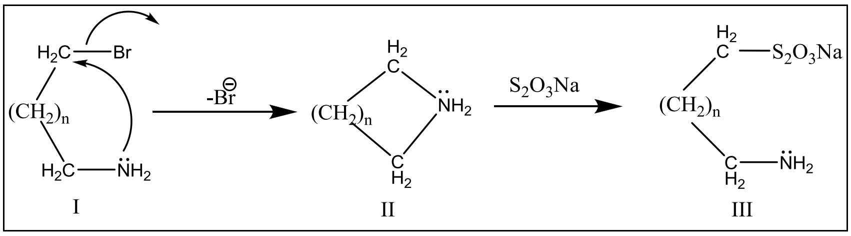

(Where n equals to 0,1,2,3,4,5,6)

Scheme 1.

From the above scheme it is clear that the two carbon atoms attached to the nitrogen in the cyclic intermediate are involved in the reaction and so called the reaction centre. This reaction centre is highly affected by the alkyl substituent on the adjacent nitrogen group which alter the electron densities of the reaction centre[9].

So that, we expect that the above neuclophilic substitution reaction is highly affected by the electron density on the reaction centre i.e by the type of substituent on the nitrogen group. For this reason quantum chemical calculations have been employed to estimate some physical properties of the reaction centre which may affect the reaction rate such as charge, bond length and angle at the reaction centre coupled with total strain energy of the reacting molecule using the general atomic and molecular electronic structure system (GAMESS) package / RHF / (3-21G) wave functions coupled with molecular mechanics calculations. The results are shown in Table 1.

Table 1 .The computed parameters of the cyclic intermediate

parameters Compounds	Charge (coloms)		Bond length (angstroms)		Bond angle (degrees)		Strain energy K cal/mol
	C_1	C_2	C_1-N	C_2-N	N-C_1-C_2	N-C_2-C_1	
aziridinium	-0.2455	-0.2457	1.5325	1.5433	61.2305	61.2801	117.9008
1,1-dimethylaziridinium	-0.2222	-0.2250	1.5127	1.5119	60.6922	60.6412	122.3626
1,1-diethylaziridinium	-0.2307	-0.2241	1.5090	1.5137	60.4958	60.8146	128.3083
1,1-diisopropylaziridinium	-0.2339	-0.2319	1.5184	1.5179	60.9491	60.9164	147.9552
azetidinium	-0.2152	-0.2151	1.5696	1.5799	89.9781	89.9525	35.2014
1,1-dimethylazetidinium	-0.1887	-0.1890	1.5547	1.5220	90.2752	90.4248	45.2139
1,1-diethylazetidinium	-0.1923	-0.1934	1.5000	1.5000	91.7961	91.7961	51.0677
1,1 diisopropylazetidinium	-0.2091	-0.2059	1.5595	1.5686	90.6917	90.1242	68.6111
pyrrolidinium	-0.2371	-0.2398	1.5610	1.5571	104.0382	103.4762	10.8035
1,1-dimethylpyrrolidinium	-0.2044	-0.2058	1.5156	1.5155	102.4412	102.2155	15.6092
1,1-diethylpyrrolidinium	-0.2053	-0.2051	1.5000	1.5000	106.1401	105.1551	29.9419
1,1diisopropylpyrrolidinium	-0.2203	-0.2174	1.5489	1.5606	105.1594	106.6636	45.6020

Referring to results in table 1 there is an increase in the charge of two carbon atoms attached to the nitrogen (C_1 and C_2)due to the replacement of the two hydrogen atoms on the nitrogen by methyl groups followed by little decreases on going from methyl substituent to isopropyl group. This decrease may be due to bulkness of isopropyl group as shown in Figure 1. On the other hand ,there is a small decrease in bond angle and length at the reaction centre C_1 and C_2 on going from un-substituted aziridinium to di-substituted pyrrolidinium. The total strain energy of molecules is increased as the bulkiness of substituent on nitrogen increases.

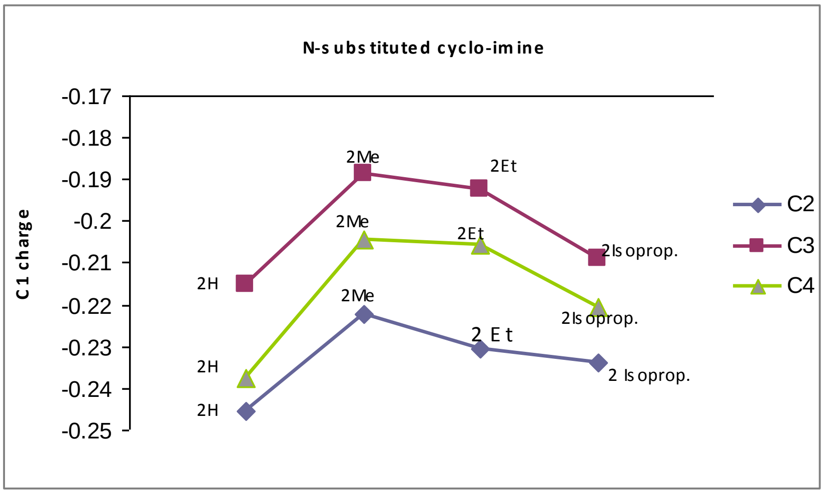

Figure 1. The variation of the carbon atom charge for N- substituted cyclocompounds

The results of a correlation analysis of the above calculated parameters with experimental values of rate constant for the reaction are demonstrated in Table 2.

Table 2: Correlation analysis of selected parameter with experimental rate constant as dependent variable of the reaction aziridinium, azetidinium, pyrrolidinium series

Compounds	aziridinium			azetidinium			pyrrolidinium		
parameters	a	b	R	a	b	R	a	b	R
C_1	-0.337	-1.592	0.988	-0.179	-1.034	0.408	-2.7E-2	-0.132	0.891
C_2	-0.313	-1.499	0.962	-0.132	-0.798	0.292	-2.75E-2	-0.134	0.942
L	-2.055	1.376	0.927	-0.389	0.270	0.260	-8.59E-2	5.71E-2	0.703
θ	-2.484	4.14E-2	0.849	-0.109	1.52e-3	0.037	2.62E-2	-2.36E-4	0.162
S	7.0E-2	-2.78E-4	0.237	-7.4E-2	2.06E-3	0.900	3.88E-3	-9.02E-5	0.613
C1 C_2	-0.342	-1.085 -0.535	0.998	0.115	18.704	0.967	5.39E-2	0.330 -0.449	0.990
C_1 L	-0.863	-1.209 0.405	0.993	-0.198	-1.011 1.52E-2	0.408	5.39E-2	-0.249 -6.95E-2	0.947
C_1 θ	-0.775	-1.380 8.011E-4	0.995	-1.368	-1.398 1.23E-2	0.486	-2.62E-3	-0.132 -2.33E-4	0.905
C_1 S	-0.314	-1.569 -1.31E-4	0.995	-0.293	-1.079 2.08E-3	0.987	-2.23E-2	-0.117 -6.44E-5	0.988
C_2 L	4.424	-5.372 -3.711	0.999	-0.307	-0.583 0.142	0.312	3.89E-2	-0.222 -5.58E-2	0.991
C_2 θ	1.607	-2.588 -3.57E-2	0.987	-1.034	-1.094 9.29E-3	0.354	-1.51E-2	-0.133 -1.17E-4	0.945
C_2 S	-0.316	-1.504 1.325E-5	0.962	-0.311	-1.146 2.19E-3	0.982	-2.28E-2	-0.118 -4.72E-5	0.988
L θ	-1.391	2.607 -4.16E-2	0.949	17.179	3.453 0.131	0.990	-7.620	5.64E-2 -7.82E-5	0.705
L S	-2.072	1.385 2.538E-5	0.927	-0.718	0.412 2.20E-3	0.972	-8.02E-2	5.48E-2 -8.53E-5	0.911
Θ S	-2.418	4.072E-2 -1.97E-4	0.866	1.367	-1.61E-2 2.44E-3	1.0	-5.39E-2	5.62E-4	0.682
C1 C2 L	-0.863	-1.209 -9.866 0.405	0.998	0.575	-20.255 20.337 -0.349	1.0	1.48E-2	0.196 -0.374 -3.39E-2	1.0
C1 C2 θ	0.421	-0.857 -1.166 -1.41E-2	1.0	-1.025	-18.517 18.635 1.17E-2	1.0	-5.07E-2	0.449 -0.565 2.60E-4	1.0
C1 C2 S	-0.327	-1.166 -0.433 -8.51E-5	1.0	-0.128	-8.268 7.837 1.32E-3	1.0	-2.23E-2	-0.117 -28.94 -6.44E-5	0.988
C2 L θ	4.196	-5.049 -3.102 -1.02E-2	1.0	-18.08	0.495 3.720 0.137	1.0	6.55E-2	-0.227 -6.02E-2 -2.01E-4	1.0

Compounds	aziridinium			azetidinium			pyrrolidinium		
parameters	a	b	R	a	b	R	a	b	R
C2 L S	4.602	-5.489 -3.841 -5.63E-5	1.0	-0.613	-0.785 0.241 2.23E-3	1.0	1.77E-2	-0.181 -3.57E-2 -2.76E-5	1.0
L θ S	-0.450	5.375 -0.128 6.45E-4	1.0	-11.32	2.374 8.423E-2 8.63E-4	1.0	-0.170	6.03E-2 7.88E-4 -1.36E-4	1.0
C1 C2 L Θ S	-0.769	-1.348 ….. …. 8.322E-3 -1.35E-4	1.0	0.523	-0.829 … … -8.55E-3 2.28E-3	1.0	-0.170	…. …. 6.03E-2 7.88E-4 -1.36E-4	1.0

N-substituent effects

It is well known from the previous studies [10,11] that a substituent has great effects on physical and chemical properties of the atom in the molecule near the substituent position.

A correlation analysis between the charge on the two carbon atoms and (k's) in a series of substituted ethylene amine gives a good correlation with the value of R is 0.988 Figure 2,then the value of R is reduced to 0.89 for substituted butyleneamine series Figure 3, and 0.166 for propyleneamine series, while a correlation of the bond length and angle with k give a value of R is equal to 0.927 and 0.89 respectively for ethylene.

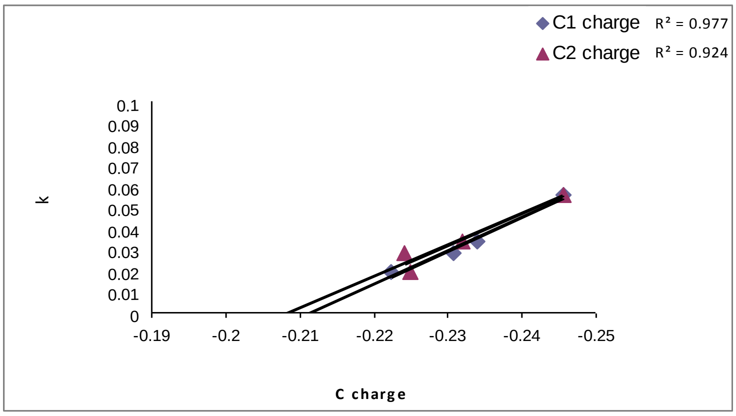

Figure 2. Correlation between k and C_1,C_2 charge for sub. C_2 cyclo-alkylamine compounds

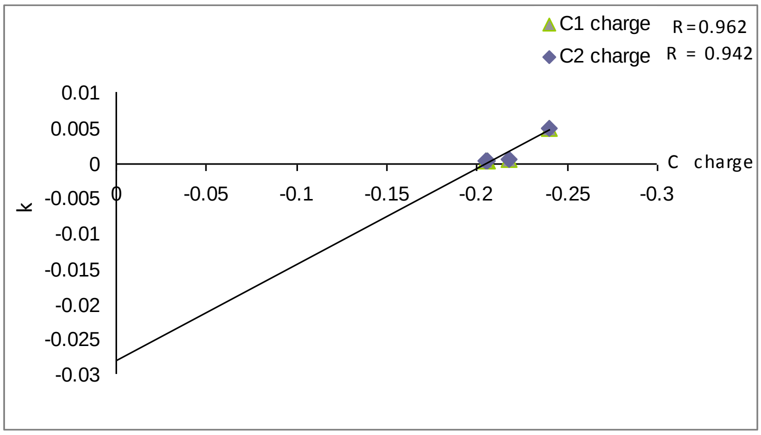

Figure 3 .Correlation between k and C_1,C_2 charge for sub. C_4 cyclo-alkylamine compounds

The strain energy in this series is less effective. on the other hand combination of two parameters leads to a good improvement in the value of R . and the value of R becomes almost near to one when more two parameters are correlated. From the above results one can extract that the experimental rate of the reaction is mainly affected by all parameters calculated for the reaction molecules.

Ring size effects

In order to estimate the effect of the ring size of the cyclic intermediate on the above mentioned we employed quantum chemical calculation to calculate the same above parameters for series of compound started from aziridinum ended to azocanium. The results of these calculations are shown in Table 3.

Table 3. A computed parameter for some cycloalkylamine

parameters	Charge at (coloms)		Bond length (angstroms)		Angle (degrees)		Strain Energy K cal/mol
compounds	C_1	C_2	C_1-N	C_2-N	C_1-C_2-N	C_2-C_1-N	
aziridinium	-0.24553	-0.2456	1.5528	1.5334	61.230	61.280	117.900
azetidinium	-0.2152	-0.2151	1.5696	1.5699	89.9781	89.952	35.952
pyrrolidinium	-0.2377	-0.2396	1.5610	1.5571	104.0382	103.476	10.8035
piperidinium	-0.2498	-0.2498	1.5404	1.5405	108.9469	108.932	6.320
azepanium	-0.2450	-0.2434	1.5396	1.5435	112.614	111.733	16.238
azocanium	-0.2362	-0.2427	1.5047	1.5044	109.300	110.819	20.161

According to Table 3 there is no clear effect at ring size on the charge of the two carbon atoms, and bond length as shown in Figure 4. On the other hand there is a clear decrease in strain energy as the ring size is increased Figure 5 . A correlation analysis of the above parameters and increase in bond angle with experimental value of the rate constant give the results shown in Table 4.

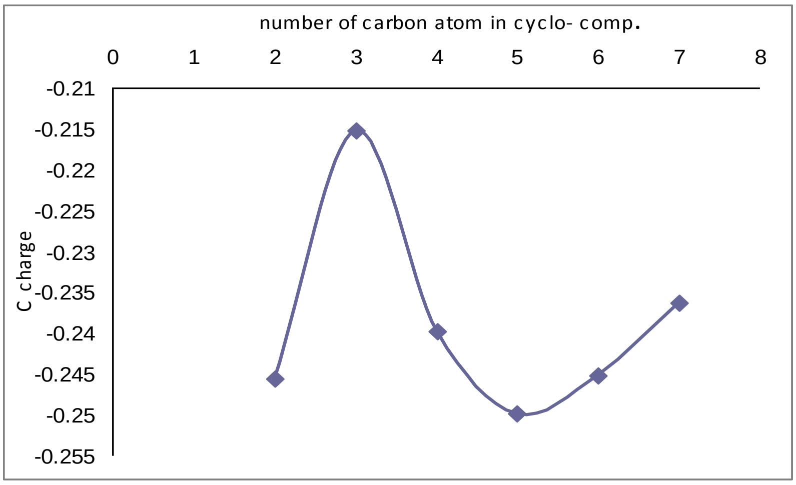

Figure 4.The variation of the carbon atom charge for un-substituted cycloamine compounds

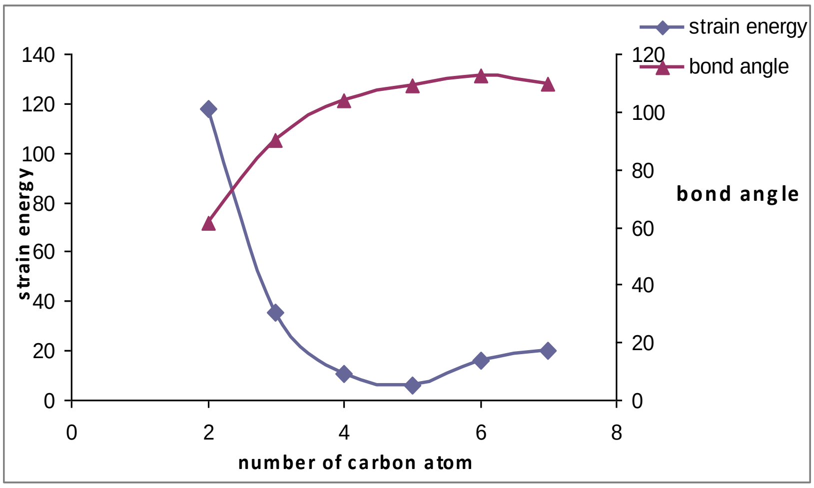

Figure 5. The variation of bond angle and strain energy with number of carbon atom

Table 4 . Correlation analysis for selected parameters with experimental values of k as dependent variable for a series of cycloalkylamine

Parameters	a	b	R	Parameters	a	b	R
C_1	-3.070E-2	-0.186	0.11	C1 C2 L	1.369	-5.737 6.397 -0.774	0.411
C_2	-1.140E-2	-0.104	0.061				
L	6.305E-2	-3.030E-2	0.033				
θ	0.114	-1.030E-3	0.958	C1 C2 Θ	3.067E-2	-0.437 7.770E-2 -1.050E-3	0.981
S	-3.500E-3	4.961E-4	0.989				
C1 C2	-1.800E-2	-1.602 1.465	0.226				
C1 L	-6.310E-2	-0.201 1.866E-2	0.111	C1 C2 S	-1.970E-2	-0.967 0.867 4.898E-4	0.998
C1 θ	3.012	-0.363 -1.050E-3	0.981				
C1 S	-2.750E-2	-0.101 4.945E-4	0.991	C2 L θ	9.274E-2	-0.316 -3.290E-2 -1.060E-3	0.980
C2 L	-2.480E-2	-0.113 7.414E-3	0.061				
C2 θ	3.291E-2	-0.353 -1.060E-3	0.980	C2 L S	-0.303	-0.231 0.158 5.042E-4	0.999
C2 S	-1.580E-2	-5.130E-2 4.956e-4	0.990				
L θ	0.327	-0.137 -1.050E-3	0.969	L Θ S	-0.334	0.179 4.841E-4 7.243E-4	0.996
L S	-0.127	8.026E-2 5.013E-4	0.993				
Θ S	1.010e-2	-1.210E-4 4.420E-4	0.990	C1 C2 L Θ S	-0.608	0.483 -0.739 0.315 5.058E-4 7.433E-4	1.0

C_1,C_2 = charge at carbon atom no.1 and no. 2, L =C-N bond length, θ= C_1-C_2-N angle, s= strain energy

The results in Table 4 show a good correlation of(k' s) with bond angle and strain energy with values of R equal to 0.958 and 0.989 respectively. The correlation of more than two parameters leads to an improvement in correlation.

Finally the correlation of the five parameters with (k' s) leads to a value of R almost is one.

Conclusion

This study of the reaction of bromoalkylamine demonstrates that quantum chemical parameters can be used successfully to account for substituent effects in addition to their ability to quantitatively relates the electronic properties of substituent to their physio-chemical effects, an attractive feature of quantum chemical parameters is that they are both flexible and interpretable. Such models can also call attention to questionable experimental values reported in the literature and encourage a re-examination of the experiments in such cases.

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تطوير عوامل جديدة ذات تأثير على سرعة التفاعل الاستبدالي للبروموالكيل أمين

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الملخص

يتضمن البحث دراسة تأثير كل من المعوضات المختلفة وحجم الحلقة للمركبات الوسطية المتكونة في التفاعل الاستبدالي للبروموالكيل امين على ثابت سرعة التفاعل. حيث تم حساب كمية الشحنة على ذرات الكربون وطول الآصرة والزوايا عند مركز التفاعل بالإضافة إلى طاقة الشد للجزيئة المتكونة وذلك بعد اختيار الشكل الهندسي الأمثل للمركبات باستخدام برنامج (chemoffice ver.11) المتضمن نظرية Hartree-Fock basis set (3-21G)/ ومن خلال ربط القيم النظرية المحسوبة أعلاه مع قيم ثوابت سرعة التفاعل العملية باستخدام تحليل انحداري (منفرد ومتعدد العوامل) أظهرت النتائج أن عامل الشحنة على ذرة الكربون هو الأكثر تأثيرا في المركبات التي تحتوي على نفس العدد من ذرات الكربون و ذات المعوضات المختلفة على ذرة النتروجين بينما نجد إن عامل الشد الحلقي هو الأكثر تأثيرا في المركبات التي تختلف في عدد ذرات الكربون في المركبات المتفاعلة.