# Additional Factors Affecting the Rate and Mechanism of Ring Opening Reaction

**Mahmoud S. Saieed**
**Chemistry Department, College of Education**
**Mosul University**

| Received | Accepted |
|---|---|
| 17/5/2005 | 17/7/2005 |

## الخلاصة

في هذا البحث تم دراسة حركية التفاعل بين الثايوسلفات ومشتقات البرومو الكيل امين ذات التركيب $RR`N-(CH_2)_n-Br$ حيث ان n تاخذ القيم 2 و 3 و 4 و 5 و 6 وان R = R` = H او مثيل او اثيل او الازوبروبيل وذلك في محلول مائي عند اسس هيدروجينية مختلفة. ان النتائج في المحيط القاعدي اعطت ادلة واضحة على ان التفاعل يسير من خلال تكوين مركب وسطي حلقي وان سرعة التفاعل تعتمد على فعالية هذا المركب الوسطي والتي بدورها تعتمد بشكل اساسي على طاقة الشد الحلقي في الحلقات الكبيرة. ان التفاعلات التي يتكون فيها حلقات صغيرة (اقل من حلقة خماسية) تكون سرعتها عالية جدا لا يمكن تعليلها على اساس الشد الحلقي فقط. فقد تم الاخذ بنظر الاعتبار عوامل اخرى مثل الكثافة الالكترونية عند ذرة النايتروجين وعامل الاعاقة عند مركز التفاعل وذلك احتمالية حدوث تفاعل ناجح وعند ادخال العوامل اعلاه اصبح بالامكان تعليل سبب السرعة العالية للتفاعلات ذات المركب الوسطي الصغير. ومن جهة اخرى لوحظ ان ميكانيكية التفاعل تختلف في الوسط الحامضي ويحدث التفاعل عن طريق المهاجمة المباشرة للنيوكلوفيل على مجموعة المثيل المرتبط بالبروم. كذلك تم دراسة سرعة التفاعل عند درجات حرارية مختلفة من اجل حساب الثوابت الثيرموداينميكية والتي استخدمت في مناقشة العوامل المؤثرة على سرعة وميكانيكية التفاعل.

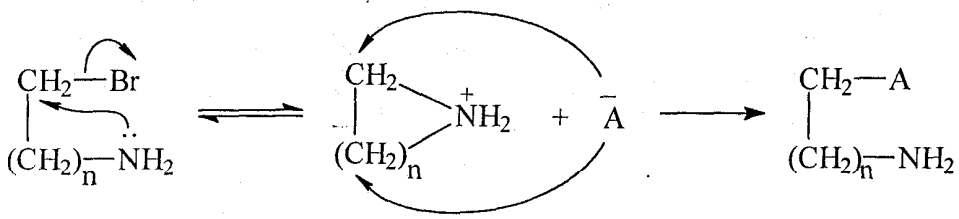
## ABSTRACT

The reactions of thiosulphate ion with some bromoalkylamines of structure $RR`N-(CH_2)_n-Br$, where n = 2,3,4,5 or 6 and R = R` = H, methyl, ethyl or isopropyl, were studied kinetically in an aqueous solution at different pH. The kinetic results for these reactions in basic medium gave explicit evidence in favour of the formation of cyclic intermediate during the reaction course. The rate of these reactions depends mainly on the reactivity of the cyclic intermediate. It has been found that the

reactivity of large ring intermediate is mainly controlled by the energy of ring strain relief. As the ring size becomes small (smaller than five members) the rate of the reaction becomes very fast and can't be explained on the bases of ring strain relief only. In order to explain this observation other factors may affect the reactivity of the cyclic intermediate are taken into account, such as the electron density at the nitrogen atom, the sterochemical situation at the reaction centre and the probability of a successful reaction. Taking into account these factors gave a better explanation for the high reactivity of small ring are given. On the other hand, it has been observed that the reaction in acidic medium proceed with a different mechanism in which the reaction occurs by a direct attackment of the nucleophile on the methylene group attached to the bromo group. The dependence of the rate constants on temperature were studied in order to estimate the thermodynamic parameters which were utilized in the discussion of the factors affecting the rate of ring opening reaction.

## INTRODUCTION

Generally, the reactions of bromoalkylamines with different nucleophilic reagents in basic aqueous medium are initiated by a reversible unimolecular cyclization reaction[1-5], which resulted from nucleophilic intramolecular replacement of the bromogroup by the neighbouring amino group producing a cyclic intermediate[6]. After that the reaction proceeds with rupturing the cyclic intermediate under the influence of the nucleophile ($A^-$) forming the product as shown in scheme 1.




**Scheme 1**

It has been found[7] that the rate of these reactions are highly depending on the reactivity of the cyclic intermediate formed in these reactions and the reactivity in most cases is related to the ring strain energy which has been proposed as a driving force in these reaction. Surprisingly, the small ring intermediate (≤ four members) undergoes the reaction at the very fast rate[8] which can hardly be explained on the bases of ring strain relief only and this reflects the presence of other factors affecting the reactivity of the small ring intermediate.

In order to assess the contribution of other factors affecting the reactivity of the cyclic intermediate formed in these reactions, the reaction between thiosulphate and the different types of bromoalkylamines having different chain length and different alkyl substituents on the amino group has been studied in this work. The dependence of the rate constants on the temperature and pH of the medium was studied and the results were utilized in the discussion of the rate and mechanism of the reaction.

## EXPERIMENTAL

**Substances**: All chemicals used in this work are of analytical grade and supplied either from Fluka A.G. or BDH Chemical Ltd.

**Apparatus**: Orien pH-meter Research model 301, UV/Vis spectrophotometer model SP-8-200 Pye Unicam and Gallen Kamp water bath 20H were used.

**Preparations**: All bromoalkylamines were prepared from the reaction of hydroalkylamine with hydrobromic acid using a previously recorded procedure[9,10].

**Kinetic measurements**: Ten milliliter of sodium thiosulfate solution (0.01 M) and 10 ml of bromoalkylamines solution (0.1 M) (both solutions were prepared using universal Britton Robinson buffered solution at wanted pH) were mixed in the reaction cell after thermostated at the desired temperature. The cell was kept at constant temperature by circulating water in its outer Jackett from the water bath. The thiosulphate ion concentration was determined by pipetting out the desired volume (one ml) and placed into a volumetric flask containing Britton Robinson buffer solution at pH equal 4.0, 12 ml of iodine solution (0.001 M) and 2.0 ml of starch solution. Then the mixture was diluted to 100 ml with same buffer solution. After shaking, the excess of iodine was determined spectrophotometrically[14].

## RESULTS AND DISCUSSION

**Kinetic treatments**: It has been found[1,2] that the reactions between bromoalkyl amines and different neucleophiles are first-order in concentration of both reactants (amines and neucleophiles) with over all second-order reaction rate. In this work all kinetic runs were carried out at pseudo first-order condition, in which the concentration of amines are always kept ten times greater than thiosulphate ion concentration. The first order plots between $\ln \frac{A_\infty - A_0}{A_\infty - A_t}$ and the time for the reaction gave straight lines as shown in Figure 1 where $A_0$, $A_\infty$, $A_t$ are the absorbance at initial, infinity and any times respectively. The rate constants were

calculated from the slops of these lines, using a least-square method. It is worth mentioning that duplicated kinetic runs showed that the results are reproducible within 2.6%. The values of the rate constants at three different pH of the media were calculated as shown in Table 1.

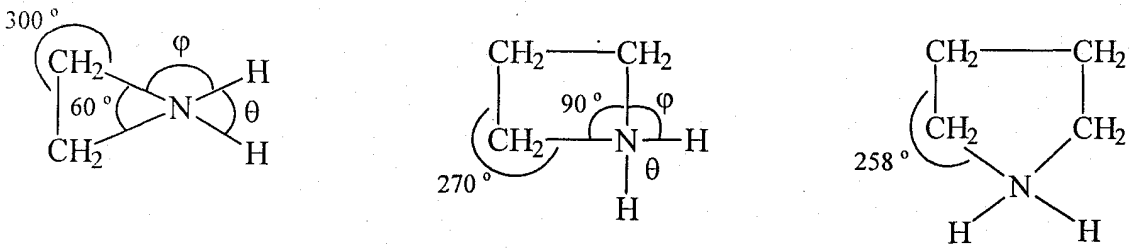
**Table 1: The values of the rate constants ($K.sec^{-1} \times 10^4$) at 60 °C; a at 15°C**

| Compound | pH of the medium | | | Strain energies[15] mol |
|---|---|---|---|---|
| | 8.9 | 7.9 | 4.9 | |
| $Br-(CH_2)_2-NH_2$ | 9.00 a | 8.4 a | 5.50 | 27 |
| $Br-(CH_2)_2-N(me)_2$ | 3.33 a | 3.10 a | 6.03 | - |
| $Br-(CH_2)_2-N(et)_2$ | 5.87 a | 5.49 a | 6.51 | - |
| $Br-(CH_2)_2-N(isopropyl)_2$ | 8.10 a | 8.00 a | 7.13 | - |
| $Br-(CH_2)_3-NH_2$ | 2.80 a | 2.6 a | 3.00 | 26 |
| $Br-(CH_2)_3-N(me)_2$ | 2.30 a | 2.18 a | 4.50 | - |
| $Br-(CH_2)_3-N(et)_2$ | 2.70 a | 2.55 a | 5.20 | - |
| $Br-(CH_2)_3-N(isopropyl)_2$ | 19.60 a | 17.60 a | 6.50 | - |
| $Br-(CH_2)_4-NH_2$ | 5.05 | 4.70 | 1.55 | 6 |
| $Br-(CH_2)_4-N(me)_2$ | 4.00 | 3.90 | 1.23 | - |
| $Br-(CH_2)_4-N(et)_2$ | 4.30 | 4.10 | 1.34 | - |
| $Br-(CH_2)_4-N(isopropyl)_2$ | 4.80 | 4.00 | 1.41 | - |
| $Br-(CH_2)_5-NH_2$ | 2.92 | 2.62 | 1.20 | 0 |
| $Br-(CH_2)_6-NH_2$ | 6.80 | 5.90 | 1.00 | 7 |
| $Br-(CH_2)_7-NH_2$ | 11.60 | 9.00 | 1.10 | 10 |

**Ring size effect on the reaction rate**: The rate constants shown in Table 1 reveal that there is a definite increase in their values as the ring strain energy of the intermediate is altered. Also a plot between $\delta$ ln K (where $\delta$ ln K represents the change in ln K relative to ln K for six member ring cyclic intermediate) and strain energy (relative to six-member ring) gave a straight line as shown in Figure IIa. This result indicates that in the reaction of these compounds the driving force is mainly controlled by ring strain relief energy. Surprisingly, small rings showed abnormal fast rate for ring opening reaction, which can be seen from the pronounced deviation from linearity as shown in Figure IIa. This observation let one believe that for small rings ($\leq$ 4 members) the strain relief energy is not the only factor affecting the ring opening rate, but there are additional factors that may also play an important role in the reaction rate such as the steric situation at the reaction centre. For example, the steric hindrance at the methylene groups is reduced as the ring size decreases as shown in Scheme II. (for ethylenimonium ion the attack angle is 300 ° out 360 °, while for propylenimonium ion the attack angle decreases to 270 ° out of 360 ° and so on). Another factor that may also be taken into

account is the probability of the successful reaction, for example in ethylenimonium ion the attackment of the nucleophile on both methylene groups during the reaction course leads to a successful reaction, i.e. the probability (s) should be equal to 2 out of three. While in reaction of propyleneimonium ion the probability of a successful reaction is two out of four. So that, there is a decrease in the probability of a successful reaction as the ring size increased. By taking the above two factors into account (the probability and the ratio of attack angle). A plot of $\delta$ ln K against the value of strain energy multiplied by the probability factor (s) and ratio of attack angle ($R_o$). A better relationship has been noticed as shown in Figure IIb. This reveals the incorporation of these factors in the reaction rate.

**Effect of N-alkyl substituents**: It is useful to note that the pKa values for large ring cyclic amines are close to each other and similar to the pKa value of a secondary amines[11], showing that the introduction of a positive charge does not change the relative stabilities of these amines. In contrast, the pKa value of small rings such as aziridine is three units lower than the secondary amines[11], so that introduction of a positive charge decreases the stability of these ammonium ions. Accordingly, the presence of alkyl group at the amino group increases the stability of the cyclic intermediate[12] by decreasing the charge on the nitrogen atom, leading to a decrease in the reaction rate. This assumption is supported by the results (shown in Table 1) which reflects a clear decrease in rate constant for the reaction in basic medium when the N-hydrogen is replaced by alkyl group. The only exception N,N-diisopropyl bromopropyl amine react faster than unsubstituted precursor. This abnormal result may be attributed to the bulk of isopropyl group which reduces the stability of the cyclic intermediate.




**Scheme II**

**The pH dependences**: The nucleophilicity[1,2] of amino group is highly pH dependent. So that the rate and mechanism of these reactions should be also depending on the pH of the medium. For this reason, these reactions have been studied at different pH and their rate constant are gathered in Table 1. A careful look at the values of the rate constants for

the reaction in basic medium reflects that their values are increased with the pH increasing. This observation is attributed to the fact that the positive charge on the nitrogen atom is increased with pH increase, resulting to a decrease in the stability of the intermediate and activating the reaction. In acidic medium, when the pH is less than pKa of the compound under investigation the case is in constant to that in basic medium. The amino group remains as a tertiary ammonium ion, so that its participation in the reaction course is forbidden and proceeding with a direct attackment of thiosulphate ion to the methylene attached to the bromide atom for this reason, a pronounce decrease in the reaction rate at acidic medium if compared with the reaction in basic medium has been noticed (see table I). On the other hand, it has been found that there is a regular decrease in the reaction rate of the compounds $Br-(CH_2)_n-NH_2$, as the number (n) increased to a maximum value of seven. In addition a plot of ln K versus the number of methylene group gives a straight line as shown in Figure IIIa. This observation is attributed to the fact that the presence of the additional methylene group increases the electron density at the reaction centre leading to a decrease in the reaction rate resulted from the repulsion force created between the nucleophile and reaction centre. On contrary the presence of dialkyl substituent on nitrogen activates the reaction. This result is explained in our previous work[4].

**Effect of temperature**: The dependence of the rate constant upon temperature was studied using Arrhenius equation. Since the plots between ln K and 1/T gave a straight lines as shown in Figure IV. The thermodynamic parameters are calculated and shown in Tables II, III and IV for the reaction at different pH.

**Table II: The values of the thermodynamic data for the reactions at pH = 8.9**

| Compound | Ea $KJmol^{-1}$ | $\Delta H^*$ $KJmol^{-1}$ | ln A | $\Delta S^*$ $Jmol^{-1}$ | $\Delta G^*$ $KJmol^{-1}$ |
|---|---|---|---|---|---|
| $Br-(CH_2)_2-NH_2$ | 65.13 | 62.65 | 20.19 | - 86.30 | 88.37 |
| $Br-(CH_2)_2-N(me)_2$ | 66.50 | 64.02 | 19.77 | - 88.60 | 90.42 |
| $Br-(CH_2)_2-N(et)_2$ | 68.50 | 66.02 | 21.16 | - 77.02 | 88.97 |
| $Br-(CH_2)_2-N(isopropyl)_2$ | 65.90 | 63.42 | 20.40 | - 83.34 | 88.25 |
| $Br-(CH_2)_3-NH_2$ | 67.20 | 64.72 | 19.87 | - 88.90 | 91.21 |
| $Br-(CH_2)_3-N(me)_2$ | 68.01 | 65.53 | 20.02 | - 86.49 | 91.30 |
| $Br-(CH_2)_3-N(et)_2$ | 69.13 | 66.65 | 20.65 | - 81.26 | 90.80 |
| $Br-(CH_2)_3-N(isopropyl)_2$ | 65.05 | 62.66 | 20.93 | - 78.87 | 85.24 |
| $Br-(CH_2)_4-NH_2$ | 75.50 | 72.53 | 19.68 | - 90.50 | 102.67 |
| $Br-(CH_2)_4-N(me)_2$ | 76.01 | 73.24 | 19.63 | - 90.90 | 103.50 |
| $Br-(CH_2)_4-N(et)_2$ | 76.52 | 73.75 | 19.89 | - 88.78 | 103.30 |
| $Br-(CH_2)_4-N(isopropyl)_2$ | 75.93 | 73.16 | 19.78 | - 89.70 | 103.03 |
| $Br-(CH_2)_5-NH_2$ | 76.07 | 73.26 | 19.35 | - 93.30 | 104.80 |
| $Br-(CH_2)_6-NH_2$ | 73.10 | 70.29 | 19.11 | - 95.30 | 102.50 |
| $Br-(CH_2)_7-NH_2$ | 71.20 | 68.39 | 18.96 | - 96.50 | 101.00 |

**Table III: The values of the thermodynamic data for the reactions at pH = 7.9**

| Compound | Ea $KJmol^{-1}$ | $\Delta H^*$ $KJmol^{-1}$ | ln A | $\Delta S^*$ $Jmol^{-1}$ | $\Delta G^*$ $KJmol^{-1}$ |
|---|---|---|---|---|---|
| $Br-(CH_2)_2-NH_2$ | 67.22 | 65.83 | 21.00 | - 78.35 | 91.39 |
| $Br-(CH_2)_2-N(me)_2$ | 68.62 | 66.23 | 20.58 | - 81.84 | 89.80 |
| $Br-(CH_2)_2-N(et)_2$ | 70.52 | 68.13 | 21.94 | - 70.53 | 90.83 |
| $Br-(CH_2)_2-N(isopropyl)_2$ | 69.60 | 67.20 | 21.94 | - 70.53 | 89.15 |
| $Br-(CH_2)_3-NH_2$ | 69.24 | 66.85 | 20.68 | - 81.10 | 92.60 |
| $Br-(CH_2)_3-N(me)_2$ | 70.04 | 67.65 | 20.85 | - 79.60 | 92.96 |
| $Br-(CH_2)_3-N(et)_2$ | 71.16 | 68.77 | 21.45 | - 74.61 | 92.64 |
| $Br-(CH_2)_3-N(isopropyl)_2$ | 68.28 | 65.89 | 22.18 | - 68.54 | 88.02 |
| $Br-(CH_2)_4-NH_2$ | 77.43 | 74.66 | 20.31 | - 85.28 | 105.80 |
| $Br-(CH_2)_4-N(me)_2$ | 78.03 | 75.26 | 20.30 | - 85.38 | 106.80 |
| $Br-(CH_2)_4-N(et)_2$ | 78.13 | 75.36 | 20.42 | - 84.37 | 106.00 |
| $Br-(CH_2)_4-N(isopropyl)_2$ | 77.92 | 75.15 | 20.32 | - 85.20 | 106.29 |
| $Br-(CH_2)_5-NH_2$ | 78.16 | 75.39 | 19.98 | - 88.03 | 107.47 |
| $Br-(CH_2)_6-NH_2$ | 75.27 | 72.5 | 19.73 | - 90.10 | 105.27 |
| $Br-(CH_2)_7-NH_2$ | 73.20 | 70.43 | 19.43 | - 92.42 | 104.04 |

**Table IV: The values of the thermodynamic data for the reactions at pH = 4.9**

| Compound | Ea $KJmol^{-1}$ | $\Delta H^*$ $KJmol^{-1}$ | ln A | $\Delta S^*$ $Jmol^{-1}$ | $\Delta G^*$ $KJmol^{-1}$ |
|---|---|---|---|---|---|
| $Br-(CH_2)_2-NH_2$ | 77.80 | 75.03 | 20.60 | - 82.88 | 102.60 |
| $Br-(CH_2)_2-N(me)_2$ | 75.88 | 73.11 | 20.00 | - 87.87 | 102.37 |
| $Br-(CH_2)_2-N(et)_2$ | 75.00 | 72.23 | 19.76 | - 89.86 | 104.92 |
| $Br-(CH_2)_2-N(isopropyl)_2$ | 73.37 | 70.60 | 19.25 | - 94.10 | 101.93 |
| $Br-(CH_2)_3-NH_2$ | 79.76 | 76.99 | 20.70 | - 82.05 | 104.31 |
| $Br-(CH_2)_3-N(me)_2$ | 78.12 | 75.35 | 20.51 | - 83.63 | 105.97 |
| $Br-(CH_2)_3-N(et)_2$ | 76.82 | 74.05 | 20.18 | - 86.37 | 105.58 |
| $Br-(CH_2)_3-N(isopropyl)_2$ | 75.51 | 72.74 | 20.81 | - 81.13 | 102.53 |
| $Br-(CH_2)_4-NH_2$ | 82.31 | 79.54 | 21.02 | - 79.39 | 105.98 |
| $Br-(CH_2)_4-N(me)_2$ | 81.87 | 79.10 | 20.57 | - 83.63 | 106.95 |
| $Br-(CH_2)_4-N(et)_2$ | 80.66 | 78.89 | 20.23 | - 85.96 | 107.52 |
| $Br-(CH_2)_4-N(isopropyl)_2$ | 79.03 | 76.26 | 19.75 | - 89.45 | 106.05 |
| $Br-(CH_2)_5-NH_2$ | 84.11 | 81.34 | 21.36 | - 76.56 | 106.84 |
| $Br-(CH_2)_6-NH_2$ | 85.15 | 82.38 | 21.54 | - 75.07 | 107.38 |
| $Br-(CH_2)_7-NH_2$ | 88.26 | 85.49 | 22.04 | - 70.91 | 109.10 |

For the reaction in basic medium a plot between the values of $\delta \Delta G^*$ ($\Delta G^*$ of the compound relative to the value of six members ring) and the strain energy gave a linear relationship when the ring size of cyclic intermediate is larger than or equal to five members, while the small ring deviated from linearly as shown in Figure IVa. On the other hand, a plot of $\delta \Delta G^*$ against the strain energy multiplied by the probability factors of successful reaction and the ratio of attacking angle, gave a better linear relation was found as shown in Figure IVb. This means that the strain energy relief is not the only factors affecting the reactivity of small ring but the probability of a successful reaction also plays an important role in ring opening reaction. This result consolidates with previous relation found between the rate constants and these factors. Also a careful look of the values of ln A given in Table II and III, reveals a decrease in their values as the ring size increases. This decrease may be due to the decrease in the probability factors of a successful reaction. On the other hand for the reaction in acidic medium a plot between $\Delta G^*$ and number methylene group shows a linear relationship with positive slope Figure IIIb again prove that the presence of methylene group deactivate the reaction.

**Energy-entropy relationship**: With regard to heats and entropies activation. Leffler[13] has pointed out that these two variables are related to each other by the following equation, where $\beta$ is the isokinetic temperaturte.

$$\Delta H^* = \Delta H_0^* + \beta \Delta S^*$$

Figure VI shows where isokinetic relationship for the reaction of bromoalkyl amines with thiosulphate ion, in acidic medium gave a good linear plots between $\Delta S^*$ and $\Delta H^*$ The calculated isokinetic temperature is 500 °K a part from the experiment temperature 333 °K which makes the calculated is isokinetic relation valid[13]. However, in basic medium a plot of $\Delta H^*$ versus $\Delta S^*$ show the absence of any compensation between them as shown in Figure VI. This means that these results can not be used for further regression analysis aiming at finding any isokinetic relation.

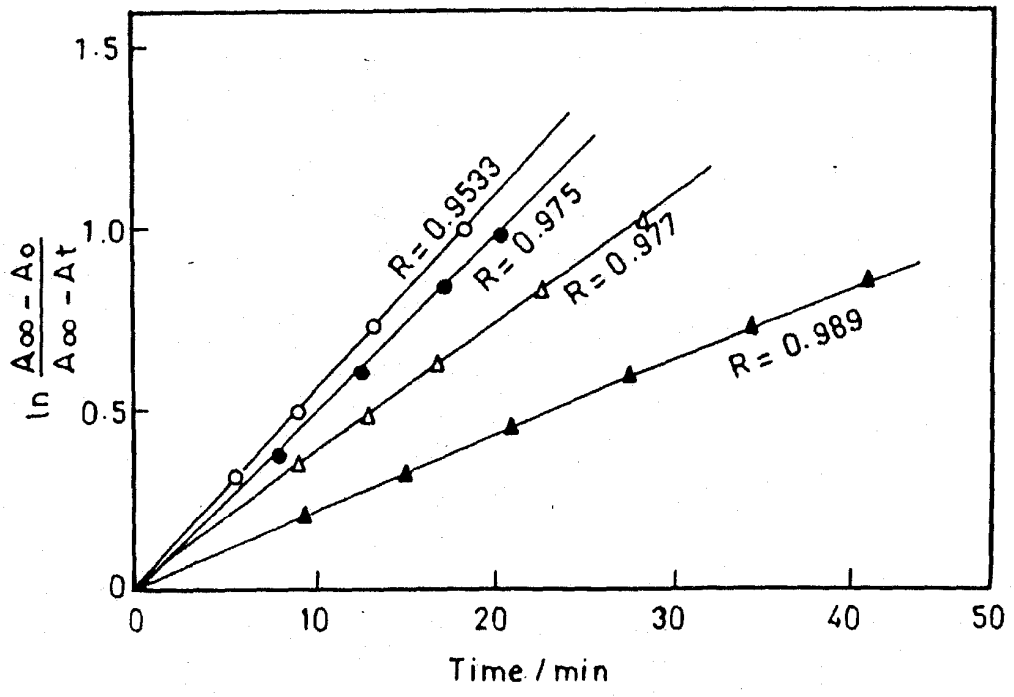



**Figure I: The first order plots for the reaction at pH=8.9 and temperature 15 °C; ○ bromoethyl amine; ▲N,N-dimethyl; △N,N-diethyl; •diisopropyl**

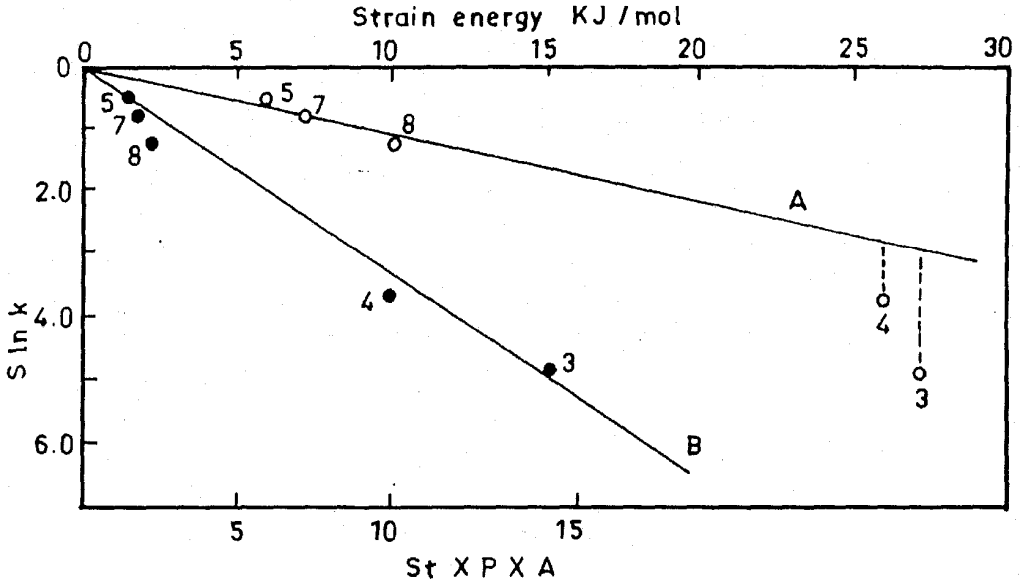



**Figure II: Plots between δ ln K and; A- strain energy; B- strain energy multiplied by the probability factor and angle ratio for ring opening reaction; The number represent the ring size**

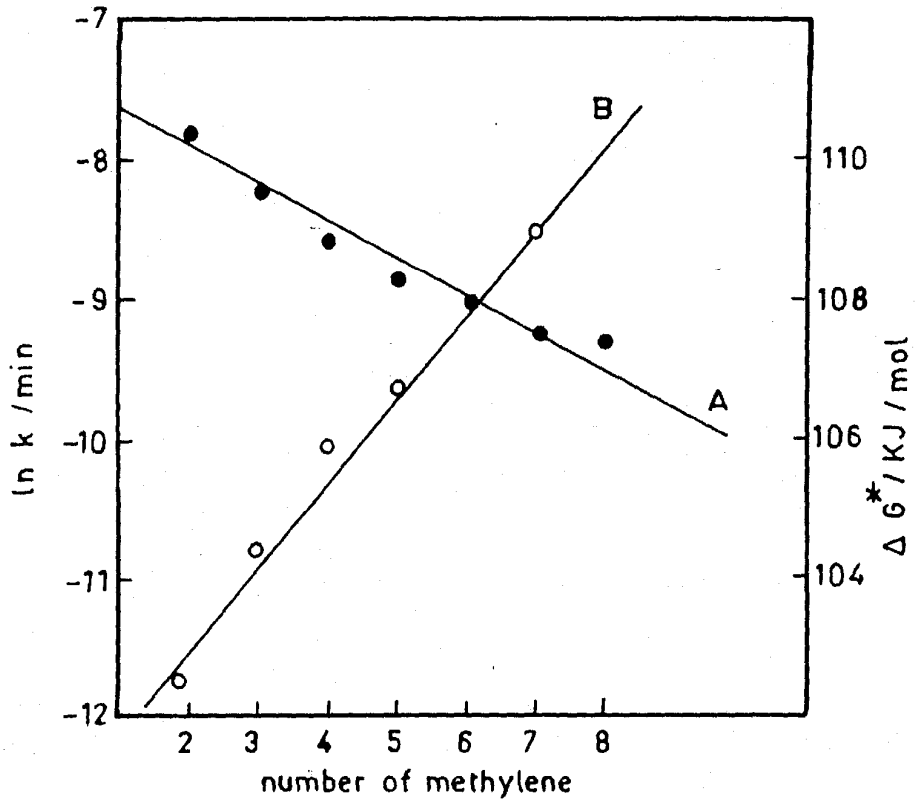



Figure III: Plots between the number of methylene group and; A- ln K; B- ΔG* for the reaction in acidic medium pH = 4.9

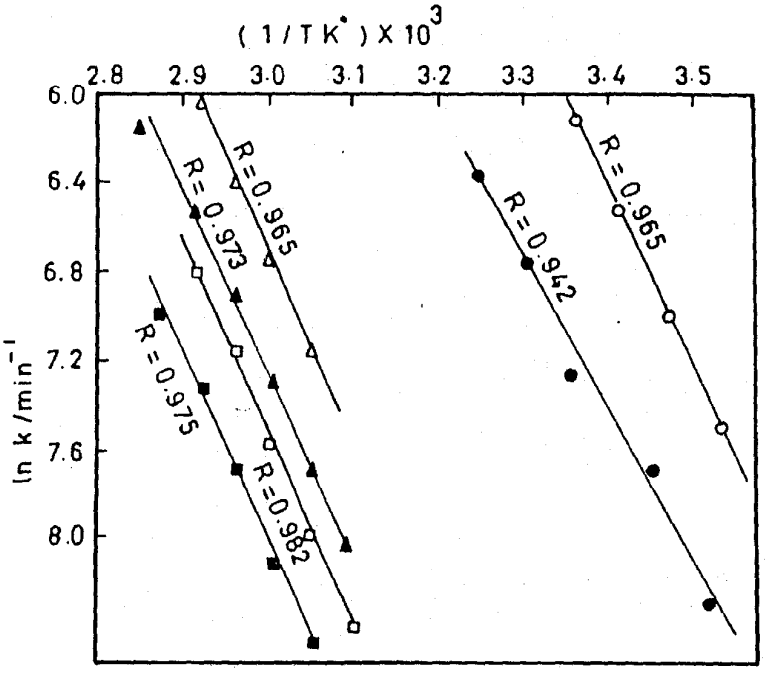



Figure IV: Arrhenius plots for the reaction of ⊙ bromoethyl amine; ■ bromopropyl amine; ○ bromobutyl amine; ▲ bromopentyl amine, □ bromohexyl amine; ⊗ bromoheptyl amine

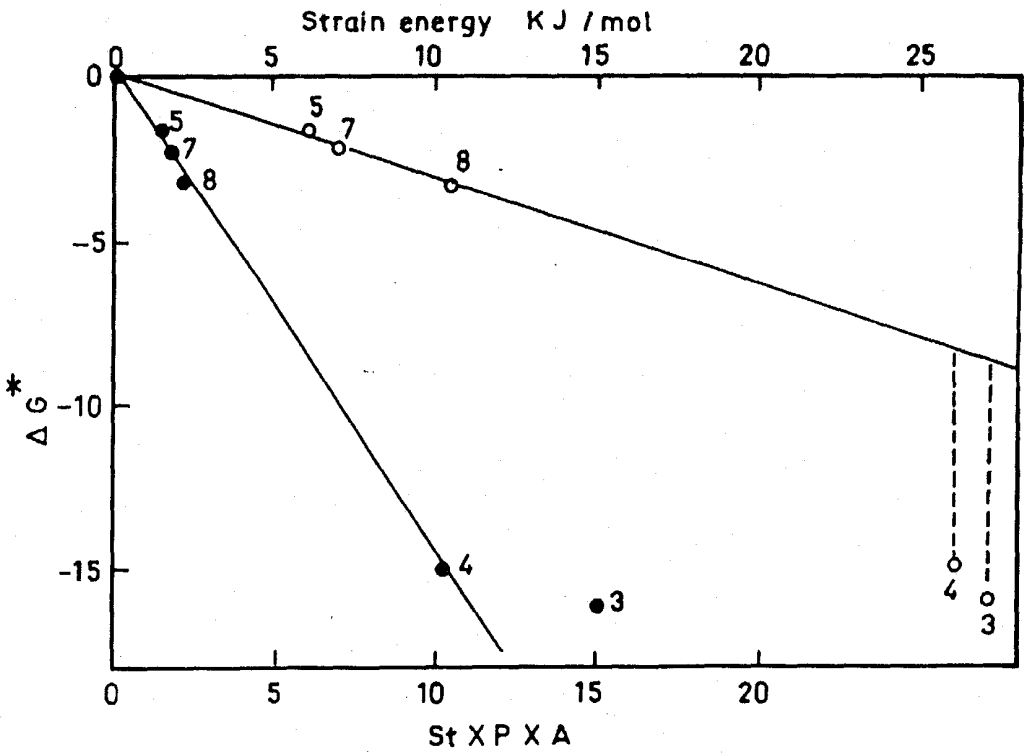



Figure V: Plots between ΔG* for the reaction and A. strain energy; B. strain x probability x angle ratio; The number is the ring size

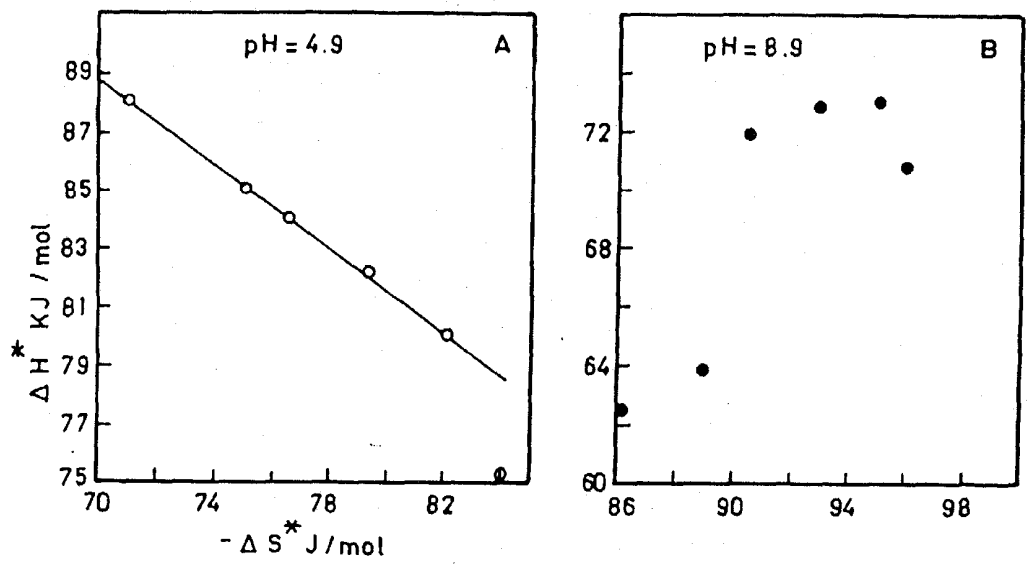



Figure VI: Plots between ΔH* and ΔS* for the reaction; A. at pH=4.9; B. at pH=8.9

## REFERENCES


1. Saieed M.S. and Al-Ghalabi N.S., Iraqi J. Sci., Vol. 31, 4(1990).
2. Saieed M.S. and Al-Ghalabi N.S., J. Edu. and Sci., Vol. 6, 8(1989).
3. Saieed M.S., Al-Ghalabi N.S. and Ahmad N.G., J. Edu. and Sci., Vol. 15, No. 39(2003).
4. Saieed M.S., Al-Imam M.M.A., J. Edu. and Sci., Vol. 14, 115-125.
5. Winnik M.A., Chem. Rev., 1981, Vol. 81, 491(2002).
6. Capon B. and McManus S.P., "Neighboring Group Participation". Vol. , Phenum Press, New York, pp. 227-260(1976).
7. Divona M.L., Illuminati G. and Lillocci C., J.C.S., Chem. Comm., 380, 1985; J.C.S., Perkin Trans. II, 1943, (1985).
8. Earley J.E., O'Roucke C.E., Clapp L.B., Edwards J.O. and Lawes B.C., J.C.S., Vol. 80, 3458(1985).
9. Goldberg A.A., J.C.S., 11, 4-5(1943).
10. Ward J.R.K., J. Amer. Chem. Soc., 57, 914(1955).
11. Rozeboorn M.D., Houk K.N., Searies S. and Seyedrezai S.E., J. Am. Chem. Soc., 104, 2448(1982).
12. Hammet L.P., "Physical Organic Chemistry". McGraw-Hill Book Co. Inc., New York, N.Y., p. 363(1940).
13. Leffler J.E., J. Org. Chem., 20, 1202(1955).
14. Vogel A.I., "A Textbook of Macro and Semimicro Quantitative Inorganic Analysis". Longman, London (1965).
15. Greenberg A. and Liebman, "Strained Organic Moleculy". Academic Press, New York (1978).