DEAMINATION OF 1-AMINOMETHYLCYCLOHEXANOL AND SOLVOLYSIS OF (1-HYDROXYCYCLOHEXYL)METHYL P-TOLUENESULFONATE

by

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ABSTRACT

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Bipinchandra T. Desai
Master of Science
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The nitrous acid deamination of 1-aminomethylcyclohexanol was carried out in aqueous phosphoric acid medium. The products, identified by gas chromatography, were cycloheptanone, 1-oxaspiro(2,5)octane, cyclohexanecarboxaldehyde, 1-hydroxymethylcyclohexanol and cyclohexanone along with three unidentified products. These were obtained in relative percentages of 1.2, 0.8, 81.1, 1.4 and 15.5, respectively. The product ratios were rationalized in terms of conformational equilibria in the intermediate diazonium cation.

The rates of solvolysis of (1-hydroxycyclohexyl)-methyl p-toluenesulfonate were measured at 95°C and 35°C in a 50% ethanol-water mixture, and were found to be much greater than the solvolysis rates of 2-hydroxypropyl p-toluenesulfonate. These results are rationalized in terms of steric strain and the neighboring group effect. The products obtained by carrying out the solvolysis in pure water at 100°C were 1-oxaspiro(2,5)octane, cyclohexanecarboxaldehyde and 1-hydroxymethylcyclohexanol. These were found in relative percentages of 22.3, 15.2, and 62.4, respectively. The differences in products and product ratios between the two reactions are discussed.

ACKNOWLEDGEMENTS

Taking this opportunity, I would like to express my gratitude and thanks to Dr. James A. Reeder for his suggestion of the problem, for his valuable guidance and for the solid encouragement he gave me throughout the course of this research.

I also wish to express my gratitude and thanks to my brother Mr. Ramanlal Desai, my mother Mrs. Kantaben Desai, Mr. Farookh Antia, Executive Officer, R. D. Sethna Trust for their financial Assistance and the encouragement they gave when it was most needed, and to Mr. Baldev Patel for helping me complete a part of my thesis.

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CHAPTER I

INTRODUCTION

Deamination of 1-Aminomethylcyclohexanol

Deamination is the reaction of primary aliphatic amines with nitrous acid. The course of deamination reactions have been cited in review articles[1,2] and books.[3,4] 1,2-Aminoalcohols have been studied extensively in the aromatic series but studies of aliphatic 1,2-aminoalcohols are relatively few. Deamination of cyclic 1,2-aminoalcohols has been reported by few workers.

The deamination of 1-aminomethylcyclohexanol has been studied by Tchoubar,[5] Smith,[6] and Favre and

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[1] J. H. Ridd, "Nitrosation, Diazotisation and Deamination," Quarterly Reviews (London), 15, 418 (1961).

[2] A. Streitwieser Jr., "An Interpretation of the Reactions of Aliphatic Primary Amines with Nitrous Acid," The Journal of Organic Chemistry, 22, 861 (1957).

[3] H. Zollinger, Azo and Diazo Chemistry (New York: Interscience Publishers, Inc., 1961) pp. 68-123.

[4] Y. Pocker, "Wagner-Meerwin Pinacolic Rearrangements in Acyclic and Cyclic Systems," Molecular Rearrangements Part I. Ed. by P. DeMayo (New York: Interscience Publishers, Inc., 1963) pp. 1-25.

[5] B. Tchoubar, "Extension of Alicyclic Rings in 1-(aminomethyl)cycloalkanols by Nitrous Acid Deaminations," Bulletin Societe Chimique De France, 216, 160-169 (1949).

[6] B. B. Smith, "The Application of the Favorski Rearrangement to the Production of A-Norsteroids and the Preparation and Nitrous Acid Deamination of 1-Aminomethylcyclohexanol," Ph.D. Dissertation, Brown University (1953).

Gravel,[7] but a detailed accounting of all the volatile products has not been reported.

The present research was undertaken to investigate the products from the deamination of 1-aminomethylcyclohexanol in detail. The products were identified and yields were obtained using a gas chromatographic technique.

Solvolysis of (1-Hydrocyclohexyl)methyl p-Toluenesulfonate

Solvolysis is a reaction in which a compound reacts with the solvent to give products. The effect of the neighboring hydroxyl group on the rates of the reaction has been reported.[8]

The solvolysis of (1-hydroxycyclohexyl)methyl tosylate has not been reported. Comparative studies of the products from deamination of 1-aminomethylcyclohexanol and that from the solvolysis of (1-hydroxycyclohexyl)methyl tosylate have not been done.

This research was therefore initiated to study the rate of solvolysis of the tosylate along with the products formed in the solvolysis. The products were identified and yields were determined by using gas chromatographic techniques.

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[7] H. Favre and D. Gravel, "Effets Stereoelectroniques Dans La Desamination Nitreuse Des tert-Butyl-4-Aminomethyl-1-Cyclohexanols cis Et trans," Canadian Journal of Chemistry, 41, 1452 (1963).

[8] H. Kalthia, "The Solvolysis of Ethylene Ditosylate and 2-Hydroxypropyl Tosylate," M.S. Thesis, Youngstown State University, 1970.

The products formed in the two analogous systems, viz., the deamination and the solvolysis, were studied on a comparative basis.

CHAPTER II

HISTORICAL

Deamination of β-Hydroxyamines

Deamination dates back to 1846 when Piria first used it in the conversion of aspartic acid into malic acid.[9] It is the reaction of primary aliphatic amine with nitrous acid. The amino group reacts with nitrous acid to give diazonium salt. This diazonium salt, being unstable, decomposes to give off nitrogen and a mixture of organic products.[10]

$$-\overset{|}{\underset{|}{C}}-NH_2 + NaNO_2 + HX \longrightarrow \left[RN_2^+\right] \longrightarrow N_2 + \begin{array}{c}\text{Mixture of}\\ \text{Products}\end{array} \qquad (1)$$

To explain the products formed after decomposition of the diazonium ion, a carbonium ion intermediate was formulated as early as 1928.[11] A complete scheme explaining the possible products is outlined in Figure 1.

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[9] Ridd, p. 418.

[10] R. T. Morrison and R. N. Boyd, Organic Chemistry, 2nd ed. (Boston: Allyn and Bacon, Inc., 1966).

[11] Ridd, p. 418.

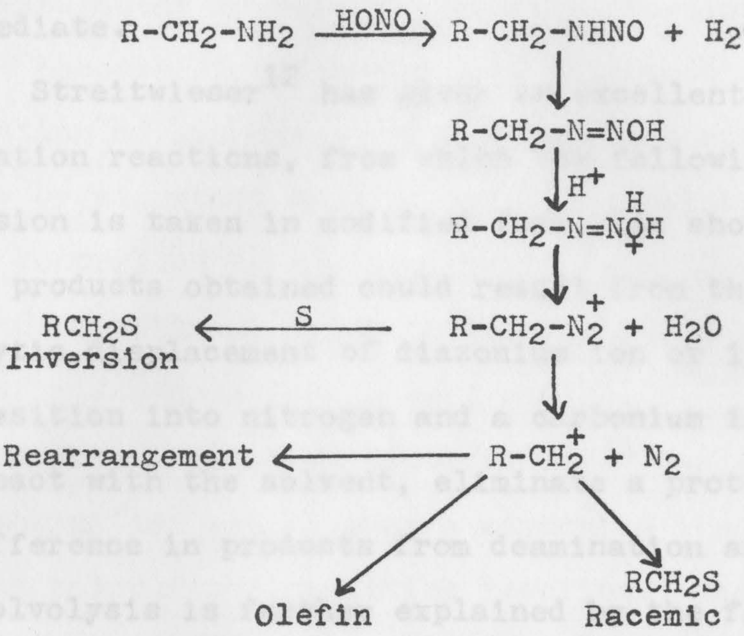

Fig. 1. Deamination.

It was subsequently noted that the products from deamination explained on the basis of carbonium ion were not the same as the corresponding products from solvolysis, which again were explained on the basis of carbonium ion intermediate.

Streitwieser[12] has given an excellent review of deamination reactions, from which the following general discussion is taken in modified form. As shown in Figure 1, the products obtained could result from the direct S_N2 solvolytic displacement of diazonium ion or its competitive decomposition into nitrogen and a carbonium ion which could then react with the solvent, eliminate a proton or rearrange. The difference in products from deamination as against that from solvolysis is further explained by the fact that the leaving nitrogen group is very stable. The activation energy required for such a decomposition of nitrogen is very small, perhaps of the order of 3-5 kcal/mole. The carbonium ion thus formed is therefore postulated to be a "high energy," "unsolvated" or "hot" carbonium ion. This hot carbonium ion has properties different from the carbonium ions formed in the solvolysis of a halide or a sulfonate ester. The solvent does not have time for the front side solvation and hence the carbonium ion is more prone to carbon skeleton rearrangement as opposed to that

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[12] Streitwieser, "Interpretation..." p. 861.

formed in solvolysis. Further it is recognized that the diazonium ion decomposes in the conformation from which it is formed, before the rotation about a C-C bond can occur. The formation of the "hot" carbonium ion is also followed by the subsequent reaction before the rotation about the C-C bond becomes significant. Rearrangement usually occurs by migration of hydrogen, alkyl or aryl groups. The mobility or migratory aptitude of the substituents is largely controlled by the conformations of the diazonium ion. The substituent trans to the diazonium group in the most stable conformation is most mobile.

On the other hand Streitwieser[13] has proposed that the diazonium ion rather than a carbonium ion is the branching point of the competing reactions. According to the theory presented, the great stability of the leaving nitrogen molecule implies that the activation energy required for the decomposition of an aliphatic diazonium ion is rather small, perhaps of the order of 3-5 kcal/mole. Thus the competing reactions which normally are not of importance become important in such a case. This is because the activation energy for the loss of nitrogen from the diazonium ion is comparable in magnitude to the activation energy for internal rotation around the C-C bond. Therefore the more stable configuration will take a route towards the products through the most easily available

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[13] Streitwieser, "Interpretation...," p. 861.

transition state, which need not be the most stable transition state. Thus a mode of reaction not observed in solvolysis reactions may be important in amine-nitrous acid reactions. It was further emphasized that because the driving force for the decomposition of an alkyl diazonium ion is the elimination of nitrogen, the rearranging group should not be regarded as providing only a neighboring group effect in the reaction, i.e. a push, but also that it is being pulled over by the positive field being generated at the α carbon atom.

The reactions which more or less account for the products in such systems are given in Figure 2.

Reaction a in Figure 2 is the direct displacement by the solvent, viz., the S_N2 process. It may be noted that this accounts for a small percentage of the inverted products.

Elimination of a proton (reaction b) is also shown to be a competing reaction. This gives rise to the various olefins observed in deamination reactions. The loss of the proton occurs through a concerted mechanism and generally such concerted eliminations result in the removal of hydrogen <u>trans</u> to the leaving group.[14]

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[14] Streitwieser, "Interpretation...," p. 861.

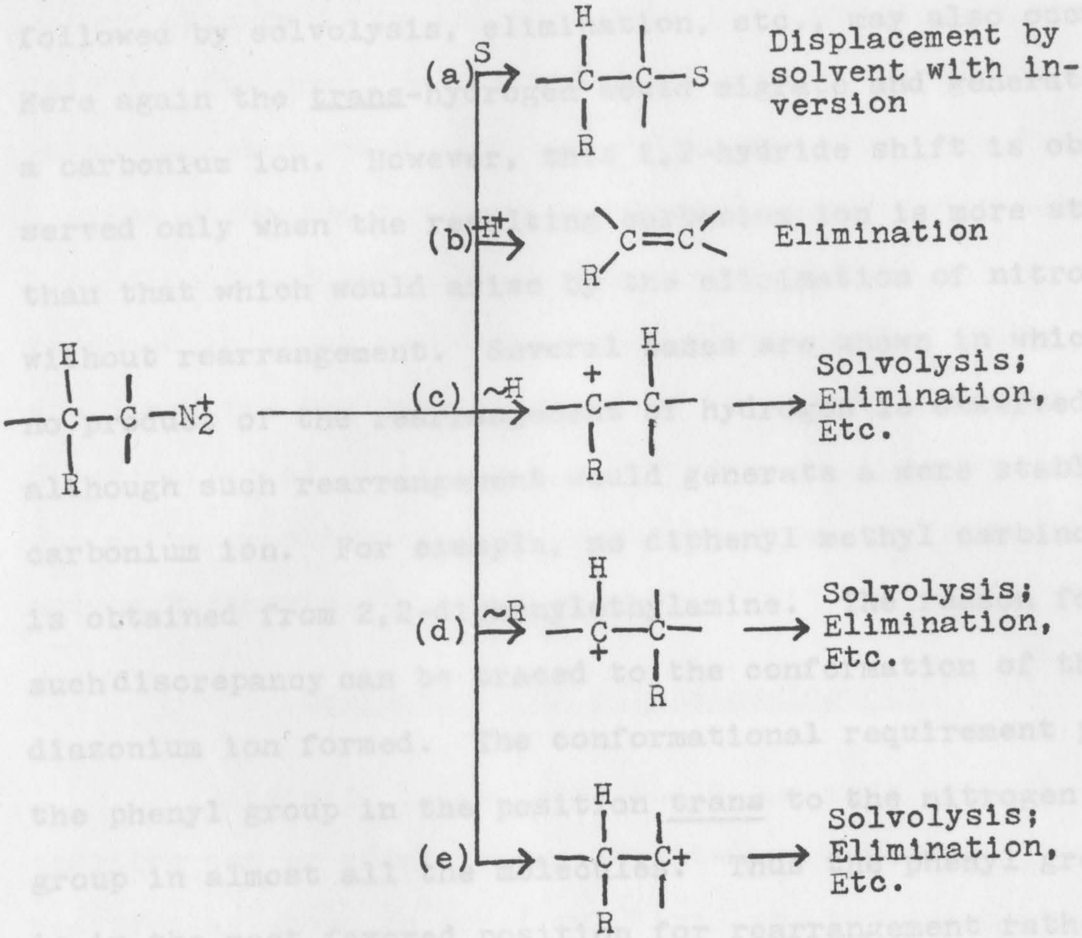

Fig. 2. Streitwieser scheme.

1,2-Hydride shift (∽H) as shown in Reaction c followed by solvolysis, elimination, etc., may also occur. Here again the *trans*-hydrogen would migrate and generate a carbonium ion. However, this 1,2-hydride shift is observed only when the resulting carbonium ion is more stable than that which would arise by the elimination of nitrogen without rearrangement. Several cases are known in which no product of the rearrangement of hydrogen is observed although such rearrangement would generate a more stable carbonium ion. For example, no diphenyl methyl carbinol is obtained from 2,2-diphenylethylamine. The reason for such discrepancy can be traced to the conformation of the diazonium ion formed. The conformational requirement puts the phenyl group in the position *trans* to the nitrogen group in almost all the molecules. Thus the phenyl group is in the most favored position for rearrangement rather than the hydrogen.

Reaction d involves rearrangement of an alkyl group (∽R) followed by solvolysis, elimination, etc. Here again as in the case of hydrogen rearrangement, conformational requirements exist and the rearrangement occurs only when the resulting carbonium ion is more stable than that which would arise without rearrangement. The conformational requirement for the 1,2-alkyl shift is the same as that for hydrogen. The rearranging alkyl group must be *trans* to the leaving nitrogen.

The final reaction as shown in the Streitwieser scheme (Figure 2) is the carbonium ion formation by the loss of nitrogen. Unlike the "high-energy" carbonium ion which has been postulated for such a reaction (see Figure 1), the carbonium ion here is considered to be "normal," i.e. directly comparable to the carbonium ions which are produced in other reactions such as solvolysis. This would require the participation of the solvent in the dissociation of diazonium ion. Further discussions of the above reaction schemes have been given by Friedman[15] and by Banthorpe.[16]

Deamination of 1,2-Aminoalcohols

In case of 1,2-aminoalcohols one more competing reaction can be added to the Streitwieser scheme. This reaction as shown in equation 2 involves the neighboring group participation by a hydroxyl group to form a protonated epoxide, which could subsequently undergo solvolysis, deprotonation, etc.

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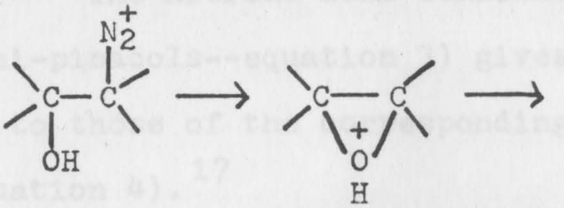
[15] L. Friedman, Carbonium Ions, Vol. II. Ed. by Olah and Schleyer (New York: Interscience Publishers, Inc., 1970) pp. 655-707.

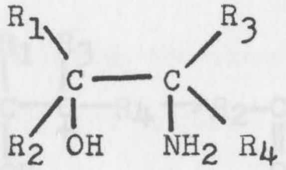
[16] D. V. Banthorpe, The Chemistry of the Amino Group, ed. by Patai (New York: Interscience Publishers, Inc., 1968) pp. 585-658.



Solvolysis;
deprotonation,
etc. (2)

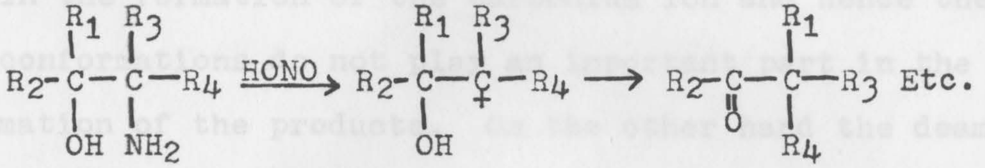
The deamination of 1,2-aminoalcohols gives a concrete example of the "hot" carbonium ion scheme and Streitwieser scheme.

The nitrous acid deamination of the number of 1,2-aminoalcohols with the general formula

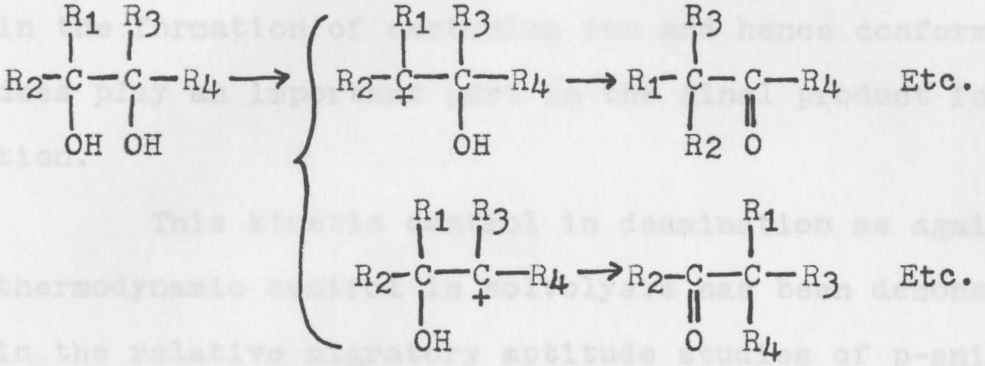


in which R_1, R_2, R_3 and R_4 represent either hydrogen atoms or alkyl, aralkyl, or aryl groups, has been investigated by many workers. However, studies of aliphatic 1,2-aminoalcohols are few. Cyclic 1,2-aminoalcohols have been of special interest due to the Tiffeneau-Demjanov rearrangement, which gives ring expansion. Although many examples are recorded, few mechanistic studies are available.

The nitrous acid deamination of 1,2-aminoalcohols (semi-pinacols--equation 3) gives rearranged products similar to those of the corresponding pinacol rearrangement (equation 4).[17]



$$R_2C(OH)(R_1)-C(NH_2)(R_3)R_4 \xrightarrow{HONO} R_2C(OH)(R_1)-\overset{+}{C}(R_3)R_4 \longrightarrow R_2C(=O)-C(R_1)(R_3)R_4 \text{ Etc.} \quad (3)$$



$$R_2C(OH)(R_1)-C(OH)(R_3)R_4 \longrightarrow \left\{ \begin{array}{l} R_2\overset{+}{C}(R_1)-C(OH)(R_3)R_4 \longrightarrow R_1C(R_3)(R_2)-C(=O)R_4 \text{ Etc.} \\ R_2C(OH)(R_1)-\overset{+}{C}(R_3)R_4 \longrightarrow R_2C(=O)-C(R_1)(R_3)R_4 \text{ Etc.} \end{array} \right. \quad (4)$$

This rearrangement can be explained by either the "hot" carbonium ion theory or the Streitwieser scheme. It should be noted that both theories essentially recognize the fact that the rearrangement takes place in the initial conformation from which the diazonium ion is formed, that the mobility of the substituents is largely controlled by the conformations of the diazonium ion and the substituent *trans* to the diazo group in the most stable conformation is most mobile.

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[17] Banthorpe, p. 585.

The relative quantities of rearrangement products from solvolysis reaction are often different from those of deamination products. The products in solvolytic rearrangements are mainly those resulting from thermodynamic control in the formation of the carbonium ion and hence the initial conformations do not play an important part in the formation of the products. On the other hand the deamination products are mainly those resulting from kinetic control in the formation of carbonium ion and hence conformation does play an important part in the final product formation.

This kinetic control in deamination as against the thermodynamic control in solvolysis has been demonstrated in the relative migratory aptitude studies of p-anisyl and phenyl groups by Curtin and Crew.[18] It was observed by Bachman and Moser[19] that, in pinacolic rearrangment of 1,2-diphenyl-1,2-di-p-anisylethylene glycol (i) with acid, the relative rate of anisyl to phenyl rearrangement is 500:1. Curtin and Crew[20] investigated the analogous reaction of 1-phenyl-1-p-anisyl-2-aminoethanol (ii) with

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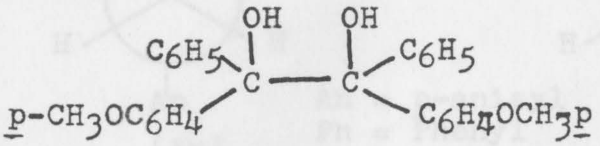
[18] D. Y. Curtin and M. C. Crew, "Migration Ratios in the Rearrangement of 2-Amino-1,1-diarylethanols." Journal of American Chemical Society, LXXVI (1954), 3719-3725.

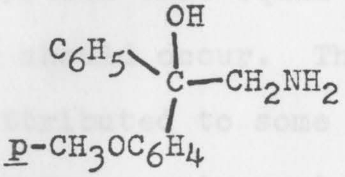
[19] W. E. Bachmann and F. H. Moser, "The Pinacol-Pinacolin Rearrangement. The Relative Migration Aptitudes of Aryl Groups." Journal of American Chemical Society, LIV (1932) 1124-1133.

[20] Curtin and Crew, p. 3719.

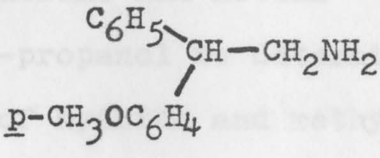
nitrous acid. They found that in this semipinacolic deamination, the relative migration ratio of anisyl to phenyl was 1.56:1.



(i)



(ii)



(iii)

In another similar semipinacolic deamination of 1-phenyl-1-p-anisyl -2- amino ethane (iii), the same migration ratio of 1.5:1 was observed for p-anisyl and phenyl groups.[21] The explanation of this has been sought in terms of the conformations of the intermediate diazonium ions. The diazonium ion would exist almost entirely in only two conformations, (iv) and (v), both equally

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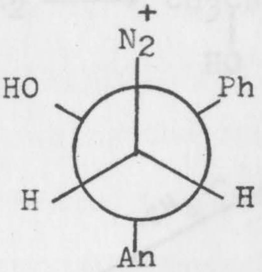
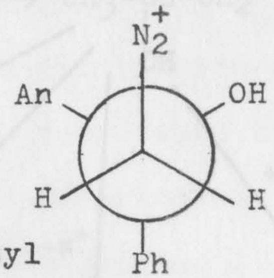
[21] L. S. Ciereszko and J. G. Burr Jr., "Migration Ratios Observed in the Reaction of Diarylamines with Nitrous Acid." Journal of American Chemical Society, LXXIV (1952) 5431-5433.

populated.



(iv)

An = p-anisyl
Ph = Phenyl



(v)

It would be expected that equal amounts of phenyl to anisyl rearrangements should occur. The slight excess of p-anisyl migration is attributed to some rotation around C-C bond which has an energy requirement comparable to the loss of nitrogen from the diazonium salt.

Tatsumi and Kotani[22] studied the deamination of 1-amino-2-propanol to determine the relative migratory aptitude of hydride and methyl groups in aliphatic hydroxy carbonium ions. The deamination products obtained were propionaldehyde (11.2%), propylene oxide (9.2%), acetone (31.1%), 1,2-propanediol (5%), 2-ethyl-5-methyl-3-nitroso-oxazolidine (19.7%) and 2,2,5,trimethyl-3-nitroso-oxazolidine (3.9%). The formation of these products was explained in terms of a "hot" carbonium ion intermediate as shown in Figure 3. A similar interpretation could also be made on the basis of the Streitwieser scheme.

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[22] C. Tatsumi and R. Kotani, "Rearrangement V.--Relative Migratory Aptitude in the Nitrous Acid Deamination of Some Aliphatic Aminoalcohols." <u>Bulletin University Osaka Prefect. Ser. B</u>, XIX (1967), 1-9.

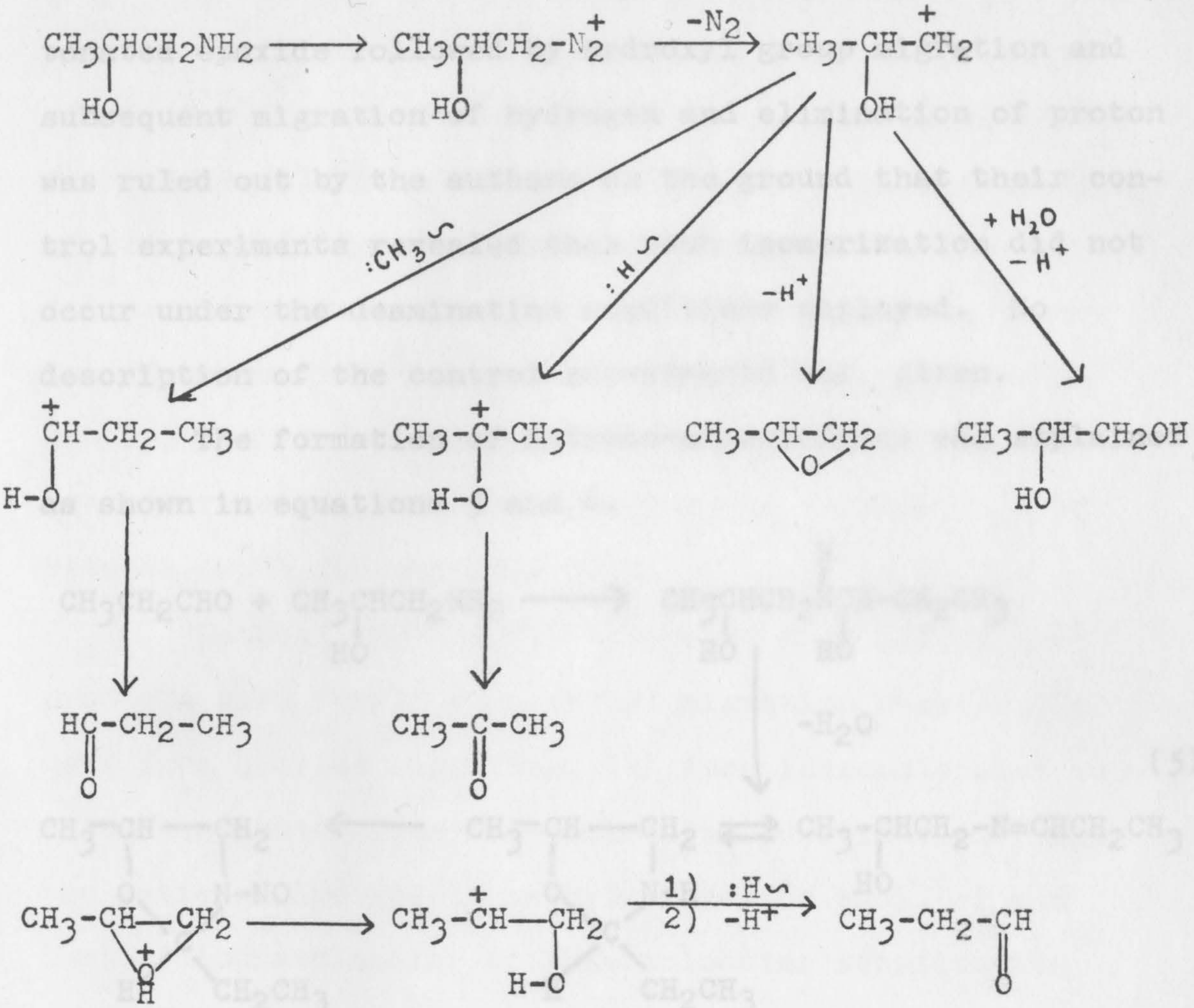
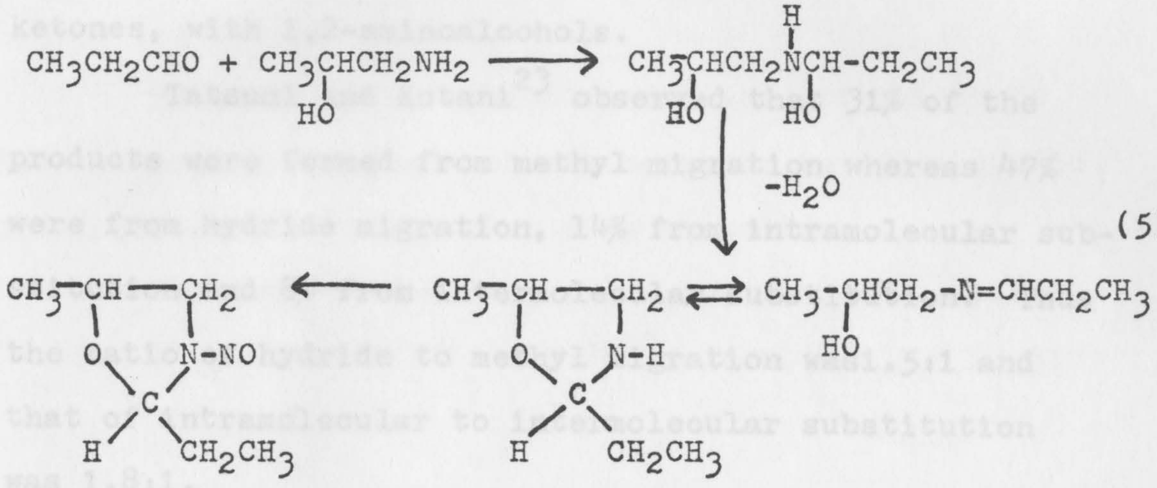
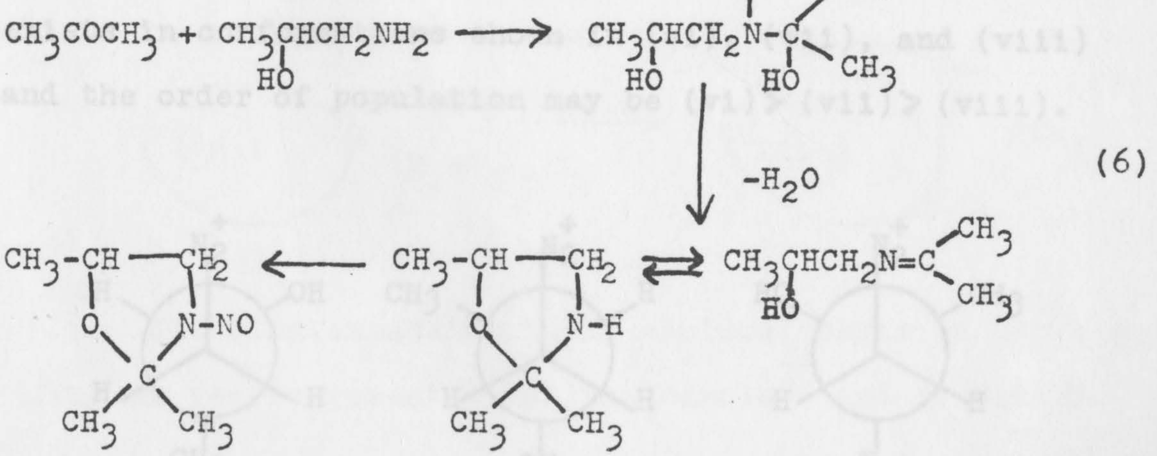


Fig. 3. Deamination of 1-Amino-2-Propanol.

The formation of aldehyde through the route of protonated epoxide followed by hydroxyl group migration and subsequent migration of hydrogen and elimination of proton was ruled out by the authors on the ground that their control experiments revealed that such isomerization did not occur under the deamination conditions employed. No description of the control experiments was given.

The formation of nitroso-oxazolidines was explained as shown in equations 5 and 6.

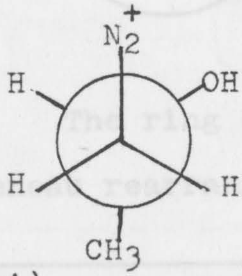

(5)


(6)

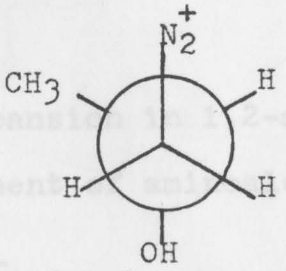
The unreacted 1-amino-2-propanol reacts with the propionaldehyde and acetone to yield addition products, which then lose a molecule of water to give oxazolidines in rapid equilibrium with Schiff bases. The nitrosation of the oxazolidines shifts the equilibrium to the right to give respective nitroso-oxazolidines and thus remove Schiff bases from the system. The greater yield of 2-ethyl-5-methyl-3-nitrosooxazolidine was attributed to greater reactivity of the aldehydes as against that of ketones, with 1,2-aminoalcohols.

Tatsumi and Kotani[23] observed that 31% of the products were formed from methyl migration whereas 47% were from hydride migration, 14% from intramolecular substitution and 8% from intermolecular substitution. Thus the ratio of hydride to methyl migration was1.5:1 and that of intramolecular to intermolecular substitution was 1.8:1.

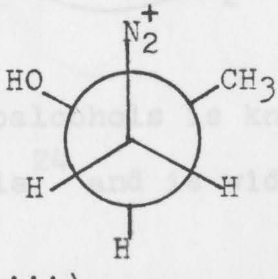
The diazonium ion formed from 1-amino-2-propanol exists in conformations shown in (vi), (vii), and (viii) and the order of population may be (vi) > (vii) > (viii).



(vi)



(vii)



(viii)

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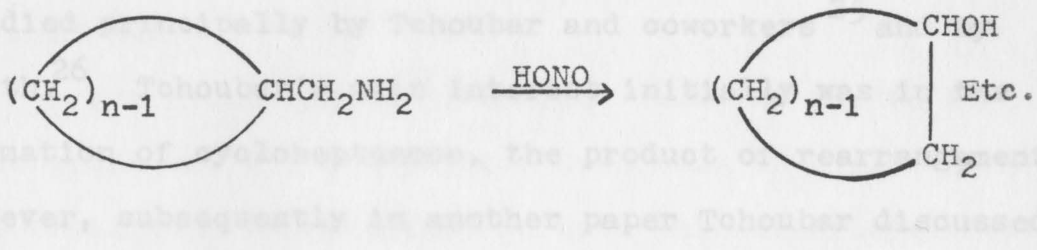
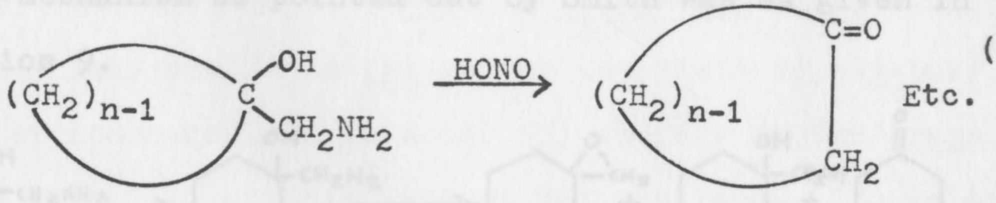
[23] Tatsumi and Kotani, p. 1-9.

The methyl group is then in the favored position for rearrangement. The observed hydride to methyl migration ratio 1.5:1 was not in accord with the relative populations of the conformations of the diazonium ion. The greater hydride migration products and lower yield of glycol was then attributed to the relative stabilities of the carbonium ions formed through rearrangement. It should be noted that this would imply greater thermodynamic control of the products as opposed to the kinetic control of the "hot" carbonium ion theory.

Deamination of cyclic amines and aminoalcohols have also been recorded. Rearrangements in this cyclic deamination often results in ring expansion.



(7)



(8)

The ring expansion in 1,2-aminoalcohols is known as Tiffeneau rearrangement of aminoalcohols[24] and is widely

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[24] Friedman, p. 655.

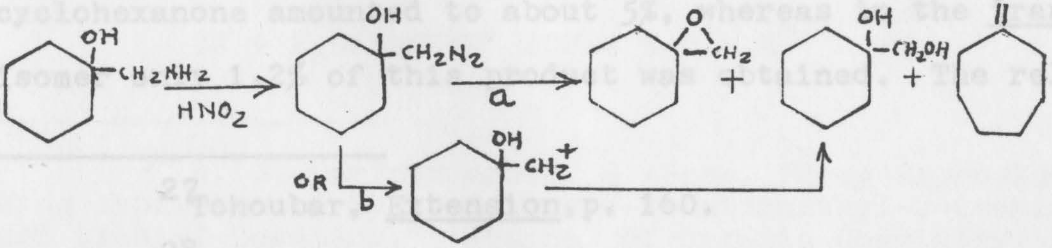
used in synthesis. This reaction has two properties favoring ring expansion:

1) No hydrogen is available at C_2 to compete with migration of ring bond electrons.

2) A protonated carbonyl group $>C^{+}-OH$ is formed on ring expansion which is comparatively stable carbonium ion. Consequently expansion is usually more complete with less olefinic by-products than in the Demjanov rearrangement of amines (equation 7).

Many deaminations of cyclic 1,2-aminoalcohols have been studied but as noted previously, few mechanistic studies are available.

Deamination of 1-aminomethylcyclohexanol has been studied principally by Tchoubar and coworkers [25] and by Smith.[26] Tchoubar's main interest initially was in the formation of cycloheptanone, the product of rearrangement. However, subsequently in another paper Tchoubar discussed the deamination in terms of pinacolic 1,2 shift. The pictured mechanism as pointed out by Smith was as given in equation 9.



(9)

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[25] B. Tchoubar, P. Weill and M. Tiffeneau, "Isomerization of Methylenecyclohexane oxide to Hexahydrobenzaldehyde and Desamination of the Corresponding Aminoalcohol to Cycloheptanone," Comptes Rendus, 205 (1937) 54-56.

[26] Smith, Thesis, pp. 1-63.

Tchoubar[27] reported a yield of 60% cycloheptanone and mentioned that the reaction mixture also contained 1-hydroxymethylcyclohexanol. The yield of this glycol was not reported and no other products were mentioned. Smith[28] reinvestigated the deamination of 1-aminomethylcyclohexanol and found that the products were 50 to 55% cycloheptanone and 6% 1-hydroxymethylcyclohexanol. He also carried out the reaction and analyzed the products, varying the pH from 4.82 to 11.75 and could not detect any epoxide. Thus it was concluded by Smith that no epoxide was formed at any stage. The nitrogen evolved from the deamination was measured. It corresponded to 86.5% of the theoretical amount. A high boiling fraction was also obtained, but was not analyzed.

Favre and Gravel[29] reported relative yields of 80% cycloheptanone, 20% epoxide and less than 1% cyclohexanone were obtained in the deamination of 1-aminomethylcyclohexanol. The absolute yields were not reported. The main object, however, was to study <u>cis</u> and <u>trans</u>-<u>tert</u>-butyl-4-aminomethylcyclohexanol. In <u>cis</u> isomer the yield of 4-<u>t</u>-butylcyclohexanone amounted to about 5%, whereas in the <u>trans</u> isomer only 1.2% of this product was obtained. The relative

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[27] Tchoubar, <u>Extension</u>, p. 160.

[28] Smith, Thesis, pp. 42-62.

[29] Favre and Gravel, p. 1452.

quantities of ring expanded ketone and epoxide were about 90:5 in cis amine and about 80:20 in the trans amine. The yields of these products were rationalized on the basis of conformational considerations.

Carlson and Behn[30] studied deamination reactions of trans 2α-aminomethyl-2β-decalol and trans 2β-aminomethyl-2α-decalol. They found that the relative yields of ring-expanded ketone and epoxide could be rationalized on the basis of steric and conformational effects in the decalin ring system.

None of these workers reported any formation of nitrosooxazolidines.

Solvolysis of Hydroxytosylates

A detailed account of solvolysis of halohydrins and tosylates has been given by Kalthia.[31] The discussion below is taken partly from his earlier account with some modifications and additions.

Solvolysis reactions are reactions involving solvent as a reagent or reactions of a compound with solvent.

$$RX + H_2O \rightleftharpoons ROH + H_3O^+ + X^- \qquad (10)$$

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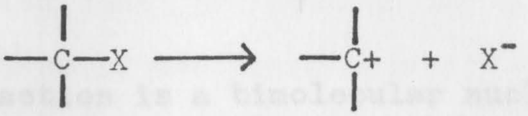
[30] R. G. Carlson and N. S. Behn, "Ring Expansions I. Ring Expansion of Epimeric trans-2-Aminomethyl-2-decalols and trans-2-Decalone," Journal of Organic Chemistry, XXXIII (1968) 2069-2072.

[31] Kalthia, Thesis, pp. 1-63.

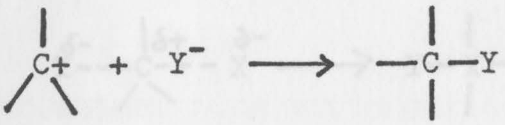
These reactions can be classified into S_N1 or S_N2 reactions, the term unimolecular solvolysis may be used almost synonymously with S_N1 reactions.[32]

An S_N1 reaction is a unimolecular nucleophilic substitution, which is considered to proceed by unimolecular dissociation to form a carbonium ion intermediate.



$$-\overset{|}{\underset{|}{C}}-X \longrightarrow -\overset{|}{\underset{|}{C}}{+} \; + \; X^- \qquad (11)$$

The carbonium ion then reacts with the solvent or the entering group in a fast step.



(12)

The rate of this reaction is determined by the slower, dissociation step. In the above equations 11 and 12, X is a leaving group such as halide or sulfonate ester, and Y^- is the entering group such as hydroxide. The rate in S_N1 reaction is dependent on the concentration of the substrate, i.e. $-\overset{|}{\underset{|}{C}}-X$, but is not dependent on the concentration of the entering group, i.e. Y^-. Thus the reaction is kinetically first order.

When the solvent is water, the S_N1 mechanism for such solvolysis may be shown as follows:

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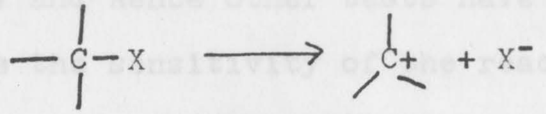
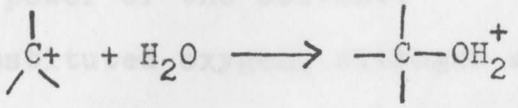
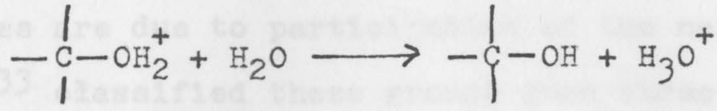
[32] C. R. Noller, Chemistry of Organic Compounds, 3rd ed. (Philadelphia: W. B. Saunders Co., 1965) p. 123.



$$-\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{X} \longrightarrow \overset{|}{\mathrm{C}}{+} + \mathrm{X}^- \tag{13}$$

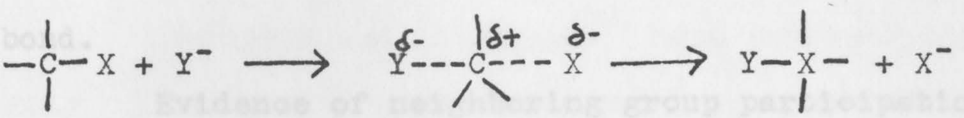


$$\overset{|}{\mathrm{C}}{+} + \mathrm{H_2O} \longrightarrow -\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{O\overset{+}{H}_2} \tag{14}$$



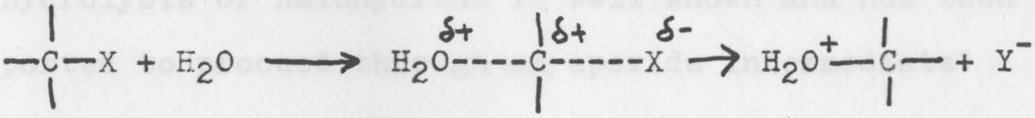
$$-\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{O\overset{+}{H}_2} + \mathrm{H_2O} \longrightarrow -\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{OH} + \mathrm{H_3O^+} \tag{15}$$

An S_N2 reaction is a bimolecular nucleophilic substitution which may be considered to proceed by direct displacement of the leaving group X by the entering group Y.

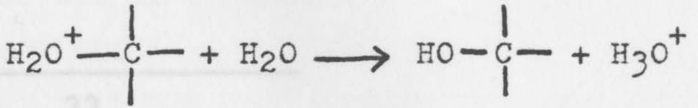


$$-\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{X} + \mathrm{Y^-} \longrightarrow \overset{\delta-}{\mathrm{Y}}\text{---}\overset{|\delta+}{\mathrm{C}}\text{---}\overset{\delta-}{\mathrm{X}} \longrightarrow \mathrm{Y}-\overset{|}{\underset{|}{\mathrm{X}}}- + \mathrm{X^-} \tag{16}$$

The rate in an S_N2 reaction is dependent on the concentrations of both the substrate $-\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{X}$ and the entering group $\mathrm{Y^-}$. Thus the reaction is kinetically second order. If the solvent is water, the S_N2 displacement can be shown as follows:



$$-\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{X} + \mathrm{H_2O} \longrightarrow \overset{\delta+}{\mathrm{H_2O}}\text{----}\overset{|\delta+}{\underset{|}{\mathrm{C}}}\text{-----}\overset{\delta-}{\mathrm{X}} \longrightarrow \mathrm{H_2O^+}-\overset{|}{\underset{|}{\mathrm{C}}}- + \mathrm{Y^-} \tag{17}$$



$$\mathrm{H_2O^+}-\overset{|}{\underset{|}{\mathrm{C}}}- + \mathrm{H_2O} \longrightarrow \mathrm{HO}-\overset{|}{\underset{|}{\mathrm{C}}}- + \mathrm{H_3O^+} \tag{18}$$

Since S_N1 is kinetically first order and S_N2 is second order, it would be possible to distinguish between the two mechanisms on the bases of kinetics. In solvolysis reaction the entering group Y is not involved and so it is not possible to distinguish between the two mechanisms kinetically and hence other tests have been devised. One of these is the sensitivity of the reaction to changes in the ionizing power of the solvent.

β-Substituted oxygen, nitrogen and sulfur containing groups increase the rate of solvolysis reaction. These increases are due to participation of the neighboring groups. Kosower[33] classified these groups into three major classes, depending on the type of electrons available for the neighboring group participation. The nonbonding or n electrons as in hydroxy or carboxy groups, the π electrons as in the C=C bond and the σ electrons as in C-H or C-C bond.

Evidence of neighboring group participation can be obtained from the study of (a) relative rates of solvolysis, (b) the stereochemistry of the reactants and products, and (c) from molecular rearrangements in the reaction.

Neighboring group participation by the β-hydroxy group has been studied by few workers. The base-catalyzed hydrolysis of halohydrins is well known and has been reported to proceed through an epoxide intermediate:

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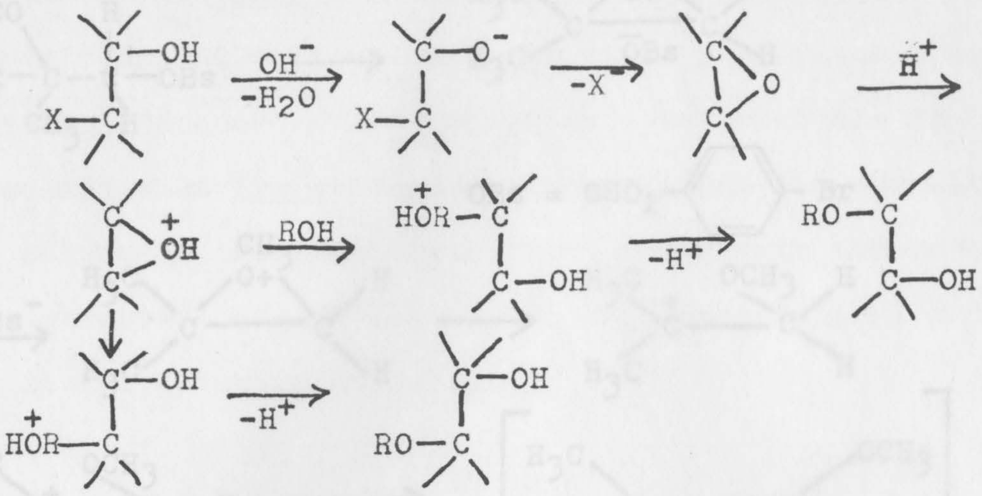
[33] E. M. Kosower, <u>An Introduction to Physical Organic Chemistry</u> (New York: John Wiley and Sons, Inc., 1968) p. 103.



(19)

Relatively little is known about the solvolysis of β-hydroxy halides and sulfonate esters in neutral media.

Winstein and Lindegren[34] have reported the solvolysis of 2-methyl-2-methoxy-1-propyl-p-bromobenzene sulfonate in 80% dioxane at 99.73°C. The main product obtained from the solvolysis reaction was isobutraldehyde in 72% yield. The reaction of 2-methyl-2-methoxy-1-propyl-p-bromobenzenesulfonate was 15 times faster than neopentyl-p-toluenesulfonate. This was reported as evidence for methoxy group participation in the rate determining ionization step. The suggested reaction mechanism for the formation of isobutyraldehyde was as follows:

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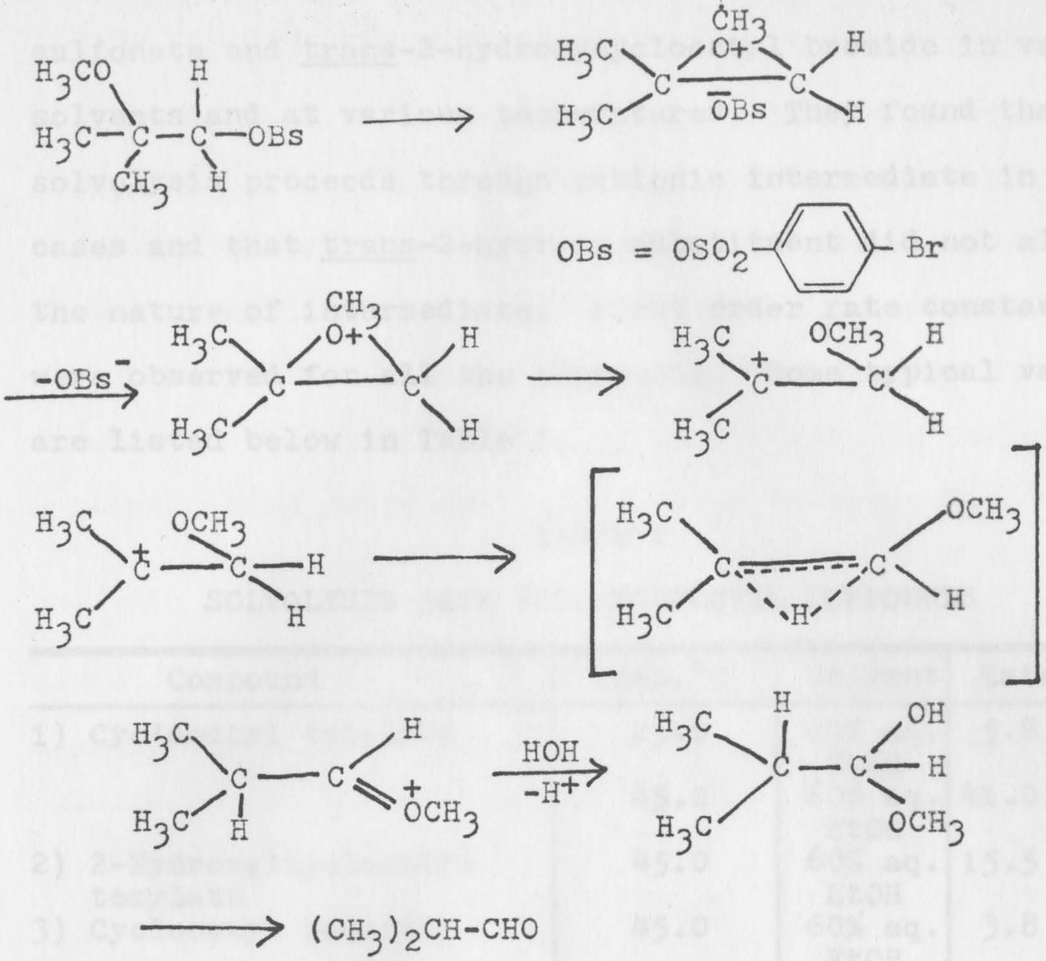
[34] S. Winstein, C. R. Lindegren and L. L. Ingraham, "Neighboring Carbon and Hydrogen. XV. Rearrangement as a Sequel to Neighboring Functional Group Participation. Solvolysis of 2-Methyl-2-Methoxy-1-Propyl-p-Bromobenzene Sulfonate." Journal of American Chemical Society, LXXV (1953) p. 155-158.



(20)

Some interesting observations were made by Roberts and coworkers[35,36] in their investigation for neighboring group effects of β-hydroxy group. Roberts and Traynham[37] studied the solvolysis of cyclooctyl-p-toluenesulfonate cyclooctyl bromide, trans-2-hydroxycyclooctyl-p-toluene-

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[35] D. D. Roberts and J. G. Traynham, "A Solvolytic Investigation of Cyclooctyl and trans-2-Hydroxylcyclooctyl Bromides and p-Toluenesulfonates," Journal of Organic Chemistry, XXXII (1967) pp. 3177-3182.

[36] D. D. Roberts, "Neighboring Hydroxyl Group Effect in Solvolysis Reaction of Common Ring p-Toluenesulfonates," Journal of Organic Chemistry, XXXIII (1968) pp. 118-123.

[37] Roberts and Traynham, p. 3177.

sulfonate and trans-2-hydroxycyclooctyl bromide in various solvents and at various temperatures. They found that the solvolysis proceeds through cationic intermediate in both cases and that trans-2-hydroxy substituent did not alter the nature of intermediate. First order rate constants were observed for all the compounds. Some typical values are listed below in Table 1.

TABLE 1

SOLVOLYSIS RATE FOR CYCLOOCTYL COMPOUNDS

Compound	Temp, °C	Solvent	Rate, sec^{-1}
1) Cyclooctyl tosylate	25.0	60% aq. EtOH	5.8×10^{-4}
	45.0	60% aq. EtOH	41.0×10^{-4}
2) 2-Hydroxylcyclooctyl tosylate	45.0	60% aq. EtOH	15.5×10^{-4}
3) Cyclooctyl bromide	45.0	60% aq. EtOH	3.8×10^{-5}
4) 2-Hydroxycyclooctyl bromide	45.0	60% aq. EtOH	1.2×10^{-5}

The k_{OH}/k_H ratio for the two tosylates at 45°C in 60% aq. EtOH solvent was 0.38. In the absence of a neighboring group effect, the inductive effect of a β-hydroxy group is expected to slow the solvolysis by a factor of 100.[38] The above k_{OH}/k_H ratio was thus attributed to a neighboring group effect.

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[38] S. Winstein and E. Grunwald, "The Role of Neighboring Groups in Replacement Reactions. XII. General Theory of Neighboring Groups and Reactivity," Journal of American Chemical Society, LXX (1948) pp. 828-837.

D. D. Roberts[39] studied the solvolysis of cyclopentyl, cyclohexyl, cycloheptyl, trans-2-hydroxycyclopentyl, trans-2-hydroxycyclohexyl, and trans-2-hydroxycycloheptyl tosylates in various solvents and at various temperatures. It was concluded by the author that an S_N1 mechanism was operative in the solvolysis of these compounds. The difference in rate was attributed to I-strain in the cyclic systems. Some rates are listed below in Table 2.

TABLE 2

SOLVOLYSIS RATES FOR SOME CYCLIC TOSYLATES AND HYDROXY TOSYLATES

Compound	Temp, °C	Solvent	Rate, sec^{-1}
1) Cyclopentyl tosylate	30.0	60% aq. EtOH	1.74×10^{-4}
	45.0	"	7.80×10^{-4}
2) trans-2-hydroxycyclopentyl tosylate	30.0	"	1.40×10^{-5}
	45.0	"	8.00×10^{-5}
3) Cyclohexyl tosylate	30.0	"	7.20×10^{-6}
	40.0	"	23.60×10^{-6}
4) trans-2-hydroxycyclohexyl tosylate	30.0	"	2.20×10^{-6}
	40.0	"	7.60×10^{-6}
	40.0	50% aq. EtOH	2.00×10^{-5}
5) Cycloheptyl tosylate	45.0	60% aq. EtOH	1.00×10^{-3}
6) trans-2-hydroxycycloheptyl tosylate	45.0	"	1.30×10^{-4}

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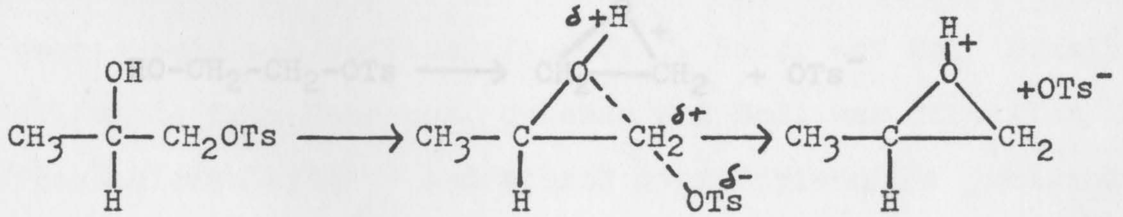
[39] Roberts, "Hydroxyl Group...," p. 118.

The k_{OH}/k_H ratio for cyclohexyl series in 60% aq. EtOH was 0.35.

Kalthia[40] studied the solvolysis reactions of 2-hydroxypropyl tosylate and ethylene di-tosylate in various solvent mixtures and at various temperatures. He reported first order kinetics for 2-hydroxypropyl tosylate. The solvent effect on rates was present but was not as great as in halohydrins. The rate constant at 95°C in 50% ethanol was 8.39 - 9.23 x 10^{-5} sec^{-1}. It was concluded that the hydroxy group in 2-hydroxypropyl tosylate exerted a neighboring group effect and significantly enhanced the rate of solvolysis in spite of the electron withdrawing inductive effect which would tend to slow the rate of solvolysis. The mechanism proposed for the solvolysis was through a protonated epoxide intermediate as shown below.



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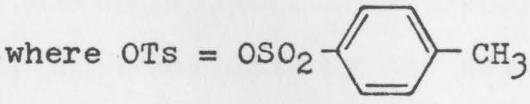

Ethylene di-tosylate also gave first order kinetics. It was also noted that 2-hydroxyethyl tosylate solvolyzed faster than ethylene di-tosylate. The rate at 84°C in 50%

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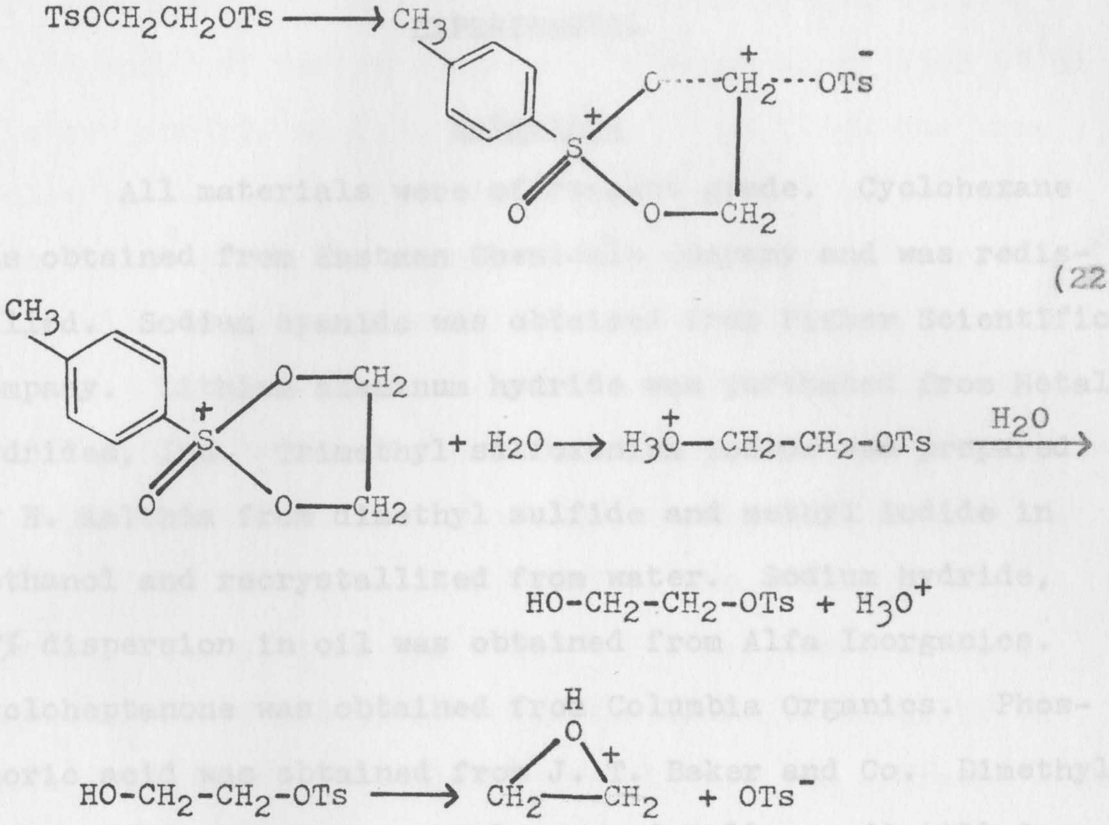
[40] Kalthia, Thesis, pp. 1-63.

EtOH was 0.361 times as fast as 2-hydroxypropyl tosylate under the same conditions. The proposed mechanism was as follows:



(22)

CHAPTER III

EXPERIMENTAL

Materials

All materials were of reagent grade. Cyclohexane was obtained from Eastman Chemicals Company and was redistilled. Sodium cyanide was obtained from Fisher Scientific Company. Lithium aluminum hydride was purchased from Metal Hydrides, Inc. Trimethyl sulfoxonium iodide was prepared by H. Kalthia from dimethyl sulfide and methyl iodide in methanol and recrystallized from water. Sodium hydride, 57% dispersion in oil was obtained from Alfa Inorganics. Cycloheptanone was obtained from Columbia Organics. Phosphoric acid was obtained from J. T. Baker and Co. Dimethyl sulfoxide from Matheson, Coleman and Bell was distilled from calcium hydride and stored over Davison 5 A molecular sieve pellets. p-Toluene-sulfonylchloride was obtained from Aldrich Chemical Company and was recrystallized from hexane. Pyridine was obtained from Fisher Scientific Company, refluxed for 17 hours using sodium hydroxide and distilled at 114°C. Absolute ethanol was distilled twice from magnesium ethoxide. The water used in kinetic studies was distilled twice from potassium permanganate in glass apparatus. The carbon-hydrogen analyses were performed by Crobaugh Laboratories, Cleveland, Ohio.

Preparation of Cyclohexanone Cyanohydrin

This procedure was modified from Organic Synthesis.[41] In a 3-neck round-bottom flask fitted with mechanical stirrer, condensor and addition funnel was placed 65.27 g (0.666 mol.) of redistilled cyclohexanone along with 60 ml of ether and 100 ml distilled water. The flask was then cooled in ice-salt bath and 82 g (1.67 mol.) of sodium cyanide was added all at once. The mixture was stirred until all sodium cyanide dissolved and the temperature reached 5°C. To this mixture, 140 ml (1.70 mol.) of concentrated hydrochloric acid was added dropwise over a period of two hours, maintaining the temperature between 5°C and 10°C. After all the acid was added, the ice bath was removed. The mixture was stirred for two hours at room temperature and 100 ml of water was added to dissolve the salts formed in the reaction. The mixture was extracted with four 50-ml portions of ether. The ether extract was then washed twice with water.

This ether extract containing cyclohexanone cyanohydrin was used directly for the preparation of 1-aminomethylcyclohexanol.

Synthesis of 1-Aminomethylcyclohexanol Hydrochloride

The procedure used was modified from that of Smith.[42] One half quantity by volume of the cyclohexanone cyanohydrin

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[41] E. L. Eliel and J. P. Freeman, Organic Synthesis, Vol. 33. Ed. by C. C. Price (New York: John Wiley and Sons, Inc., 1953) pp. 7-10.

[42] Smith, Thesis, pp. 42-62.

in ether (0.333 mol. assuming 100% conversion to cyanohydrin) from the above preparation was used. The reaction was carried out under a dry nitrogen atmosphere.

In a 3-neck round-bottom flask equipped with a stirrer, reflux condenser, addition funnel and dry nitrogen inlet was placed 25.27 g (0.666 mol.) of lithium aliminum hydride and 477 ml of anhydrous ether was added through the funnel. The mixture was stirred to form a slurry of lithium aluminum hydride. To this well-stirred slurry was added 0.333 moles of cyclohexanone cyanohydrin in 155 ml ether over a period of one hour, keeping the flask cooled in ice bath throughout the addition. The mixture was stirred overnight at room temperature.

The mixture was then treated with 25 ml water initially, followed by 14 ml of 20% sodium hydroxide and then 57 ml of water to destroy the excess lithium aluminum hydride. The resulting mixture was filtered, and the filtrate was dried over magnesium sulfate. The residue from filtration was digested with 210 ml of benzene and then filtered off. This filtrate was also dried over magnesium sulfate. The ether and benzene fractions were combined and the solvents were removed by distillation leaving crude 1-aminomethylcyclohexanol.

The crude 1-aminomethylcyclohexanol was dissolved in 277 ml of 10% hydrochloric acid. The solution was then evaporated to dryness using a vacuum evaporator to give 13.5 g of crude hydrochloride of 1-aminomethylcyclohexanol. This was recrystallized from isopropanol to yield

7.07 g of the hydrochloride as pure white crystals, m.p. 216°C. Lit.: 215-216°C.[43] Concentration of the isopropanol after filtration gave a second crop of 2.45 g of the hydrochloride, m.p. 214.5 - 215.5°C. The overall yield was 18%.

Synthesis of 1-Oxaspiro(2,5)octane

This compound was prepared from cyclohexanone and dimethylsulfoxonium methylide by the general procedure of Corey and Chaykovsky.[44] The apparatus consisted of a 3-neck round-bottom flask provided with a stirrer, reflux condenser, addition funnel and dry nitrogen inlet. The assembly was dried with a flame, in a current of dry nitrogen and the reaction was carried out under a dry nitrogen atmosphere.

Sodium hydride (12.6 g of 57% dispersion, 0.30 mol.) was placed in the 3-neck flask and was washed with 125 ml of hexane. The mixture was stirred for a few minutes and decanted. The remaining hexane was evaporated under the dry nitrogen atmosphere and 180 ml of dimethyl sulfoxide was added. This mixture was heated to 70°C and stirred at 70°C for two hours. At this stage the hydrogen evolution was complete and dimethyl-sulfinyl carbanion was formed.

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[43] Tchoubar, "Extension...," p. 160.

[44] E. J. Corey and M. Chaykovsky, "Dimethyloxosulfonium Methylide and Dimethylsulfonium Methylide. Formation and Application to Organic Synthesis." Journal of American Chemical Society, LXXXVII (1965) pp. 1353-1364.

To this solution was added 66 g (0.3 mol.) of trimethylsulfoxonium iodide. The stirring was continued for 30 minutes. The solution was kept cooled in an ice bath during the addition of the trimethylsulfoxonium iodide.

Cyclohexanone 19.6 g (0.2 mol.) was added dropwise over a period of 20 minutes, keeping the reaction mixture cooled in an ice bath. The mixture was then stirred at room temperaturefor 18 hours and at 50°C for one hour.

After cooling the mixture was poured into 400 ml of cold water and extracted with seven 100 ml portions of ether. The combined extracts were washed once with 50 ml of water and dried over magnesium sulfate. The solvent was removed by evaporation and the residue was distilled to give 11.70 g of product, b.p. 147-148°C; n_D^{25} 1.4491. Lit.:[45] b.p. 46-49°C/21 mm; n_D^{20} 1.4490.

Synthesis of 1-Hydroxymethycyclohexanol[46]

Glacial acetic acid (6 g) was placed in a round-bottom flask equipped with a magnetic stirrer and attached to a condenser. To the flask was added 75 ml of water and about 2 g of sodium acetate to adjust the pH to about 4.6. To this solution was added 5.59 g (0.05 mol.) of 1-oxaspiro-[2,5]octane from the previous preparation. The reaction mixture was stirred 24 hours at room temperature.

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[45] Smith, Thesis, p. 58.

[46] Smith, Thesis, p. 58.

The mixture was then saturated with potassium carbonate and extracted several times with ether. The combined ether extract was dried over magnesium sulfate and the ether was evaporated over a steam bath using a vacuum evaporator. After cooling, the residue solidified to give a grayish-white solid. This was recrystallized from hexane to give pure white crystals. The product was dried over phosphorus pentoxide under vacuum. The yield of 1-hydroxymethylcyclohexanol was 2.70 g (42.5%), m.p. 69-70°C. Lit.: 68-72°C.

Synthesis of Cyclohexanecarboxaldehyde

1-Oxaspiro 2,5 octane 6.01 g (0.054 mol.) was placed in a 50 ml flask fitted with a reflux condenser. To it was added 15 ml of concentrated hydrochloric acid. A large amount of heat was liberated during the addition. The mixture was then refluxed for 30 minutes.

The mixture was poured into a 200-ml beaker, half-filled with ice. When the ice had melted away, the resulting mixture was extraced with three 50-ml portions of ether. The water portion after extraction was discarded. The ether extract was washed three times with 50-ml portions of water and dried over magnesium sulfate. The ether was then distilled off. The remaining solution was subjected to fractional distillation under vacuum, using a 15-cm column filled with glass helices. At 26 mm pressure three fractions were collected. The first fraction weighed 0.3463 g and was collected between 66°C to 70°C. The second fraction weighed 0.7028 g and was collected between 74°C and 85°C. The third fraction weighed 0.9671 g and was collected between 90°C to 100°C.

The infrared spectra and gas chromatograms of all three fractions were taken and it was concluded that fractions 1 and 2 were mostly aldehyde with a small amount of 1-hydroxymethylcyclohexanol. The third fraction was mostly 1-hydroxymethylcyclohexanol. The reported boiling point of cyclohexanecarboxyaldehyde is 75-78°/ 20 mm pressure.[47]

Synthesis of (1-Hydroxycyclohexyl)-Methyl p-Toluenesulfonate

This compound was prepared in a manner similar to that used by Kalthia[48] for the preparation of 2-hydroxypropyl p-toluenesulfonate.

In a 25-ml 3-neck flask equipped with a magnetic stirrer, condenser and dropping funnel was placed 1.30 g (0.01 mol.) of 1-hydroxymethylcyclohexanol dissolved in 5 ml of pyridine. The mixture was stirred and cooled in an ice-acetone bath. To this cooled mixture was added 1.90 g (0.01 mol.) of p-toluenesulfonyl chloride in 5 ml of pyridine over a period of two hours. The mixture was maintained at -7 to -8°C with stirring during the addition. After the addition, the mixture was stirred for 30 minutes at -7 to -8°C and warmed to room temperature. It was further stirred for 30 minutes at room temperature. The mixture was then poured into a 200-ml beaker three-

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[47] Dictionary of Organic Compounds, 4th Revised ed., II, Ed. by G. Harris (New York: Oxford University Press, 1965) p. 781.

[48] Kalthia, Thesis, pp. 1-63.

fourths full of ice. The ice was allowed to melt and the mixture was extracted with four 50-ml portions of ether. The ether extract was dried over magnesium sulfate and the ether was evaporated using a vacuum evaporator. The residue was colorless oil. This was dissolved in 200 ml of n-pentane, cooled and scratched to give 1.520 g of the tosylate, m.p. 41.5 - 42.5°C. The crystals were dried over sodium hydroxide pellets under vacuum. The filtrate was concentrated to give a second crop of 0.8477 g of the tosylate. The overall yield was 83.3%. I.R. bands were at 670, 812, 835, 900, 980, 1100, 1180, 1190, 1380, 1450, 2940, and 3610. Anal. Calc. for $C_{14}H_{20}O_4S$: C, 59.13%; H, 7.0%. Found: C, 59.23%; H, 7.40%.

Calibration of Gas Chromatograph

An F and M Laboratory chromatograph Model 700 was used. The instrument was equipped with a flame ionization detector, external temperature programming control and Sargent S.R.G. recorder with disc integrator. Helium was used as carrier gas. The flow rate of helium was 40 ml/min. The columns used were 0.125" x 72" with silicone liquid phase, No. 10% UC-W98-80-100-S. The column temperature was maintained at 85°C isothermally for 15 minutes after injection, followed by a programmed rise at 10°C/min. up to 200°C. The recorder range was 1 mv. The injection port temperature was 250°C and the detector block temperature was 180°C to 210°C.

After adjusting the flow rate and temperature of the inlet, column and the detector, various samples of the possible products were run on the gas chromatograph. A retention time for each compound was established as reported in Table 3.

TABLE 3

RETENTION TIMES OF KNOWN COMPOUNDS

Compound	Retention Time in Minutes
1) Cycloheptanone	5.4
2) 1-Oxaspiro(2,5)octane	3.7
3) Cyclohexanecarboxaldehyde	6.5
4) 1-Hydroxymethylcyclohexanol	11.8
5) Octanol	8.2

To calculate the response factor for each with respect to the standard octanol, mixtures M-1 through M-6 were prepared using the quantities shown in Table 4.

TABLE 4

MIXTURES FOR RESPONSE FACTORS

Compounds	M-1	M-2	M-3
Cycloheptanone	0.600 g	0.4042 g	0.8052 g
1-Hydroxymethyl-cyclohexanol	0.100 g	0.2039 g	0.2500 g
Octanol	0.100 g	0.1000 g	0.1132 g
Chloroform	------	0.1280 g	0.3126 g

Table 4 (continued)

Compounds	M-4	M-5	M-6
1-Oxaspiro(2,5)octane	0.1014 g	0.1158 g	0.1037 g
Octanol	1.0071 g	2.5076 g	5.0033 g

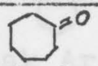
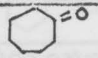
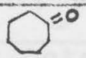
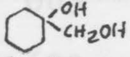
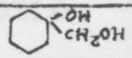
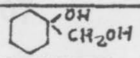
These mixtures M-1 through M-6 were then run through the gas chromatograph and the results were used to calculate the response factor for each compound. Ratios of the peak area of the compound to the peak area of octanol and weight of the compound to weight of octanol were measured. The area ratio was then divided by the weight ratio to give the response factor for the compound, relative to octanol. The response factor data is reported in Table 5. The response factor for cyclohexanecarboxaldehyde was assumed to be 1.00.

Deamination of 1-Aminomethylcyclohexanol With Nitrous Acid

Into a 10-ml round-bottom flask equipped with a magnetic stirrer, a condenser and a 1 ml calibrated dropping pipet was placed 0.745 g (0.00450 mol.) of the hydrochloride of 1-aminomethylcyclohexanol. This was dissolved in 5 ml of 1 M phosphoric acid (0.005 mol.). The mixture was cooled in an ice bath and stirred for 30 minutes. To this cooled mixture was added 1.00 ml of 5.5 M sodium nitrite (0.0055 mol.). The addition was carried out dropwise over a period of two hours with continuous stir-

TABLE 5

RESPONSE FACTORS

Sample No.	Run No.	 Peak Area	Octanol Peak Area	Area  / Area Octanol	Weight  / Weight Octanol	Response Factor[a]
M-1	1	10,100	1640	6.1585	5.9400	0.9758±0.015[b]
	2	9,400	1470	6.3945	5.9400	
M-2	1	9,580	2383	4.0201	4.0015	
	2	7,700	1765	4.3626	4.0015	
M-3	1	13,840	2092	6.6150	7.0419	
	2	15,000	2182	6.8744	7.0419	
Sample No.	Run No.	 Peak Area	Octanol Peak Area	Area  / Area Octanol	Weight  / Weight Octanol	Response Factor
M-1	1	826	1640	0.5030	1.0000	0.7530±0.1208
	2	768	1470	0.5224	1.0000	
M-2	1	3,078	2383	1.2916	2.0390	
M-3	1	3,038	2092	1.9521	2.2084	
	2	2,880	2182	1.3199	2.2084	

ring, using a calibrated pipet and keeping the solution at ice-bath temperature. Stirring was continued for one hour at ice-bath temperature and for another one hour at room temperature. During the addition of the last 15 drops of sodium nitrite some NO_2 was evolved as a brown gas.

The mixture was then extracted with seven 5-ml portions of ether. The ether extract was dried over magnesium sulfate. The ether was removed by distillation through a 15-cm column packed with glass helices, leaving the products in the form of a dark yellow oil. This mixture of products was run through the gas chromatograph for identification. Then 0.0345 g of redistilled octanol was added as an internal standard, and the products were again run through the gas chromatograph.

The water portion after extraction of products with ether was treated with 4 ml of 20% sodium hydroxide. This solution was then extracted with ten 10-ml portions of ether. The ether was distilled off using a 15-cm column filled with glass helices. The residue, consisting mainly of aminoalcohol which did not undergo deamination, was then mixed with 50 ml of 95% ethanol and 200 ml water. This mixture was titrated against 0.1 N hydrochloric acid using a methyl orange indicator. 32.4 ml of hydrochloric acid was used up in the titration.

A second deamination was run using the same procedure and the same amounts of aminoalcohol and phosphoric acid, and 1 ml of 5.00 M sodium nitrite (0.005 mol.). The products were again run through the gas chromatograph before and after adding octanol as an internal standard. The back titration with hydrochloric acid was also carried out; 30.1 ml of hydrochloric acid was used up in this titration.

Solvolysis of (1-Hydroxycyclohexyl)-methyl p-Toluenesulfonate

Kinetic Measurements

Aqueous ethanol (50%) was prepared by volume at room temperature. A stock solution was prepared by weighing out 0.2844 g of (1-hydroxycyclohexyl)methyl tosylate into a 100-ml volumetric flask and made up to the mark with the required quantity of 50% ethanol.

For the rate at 95°C, the above stock solution was prepared at room temperature. Pipetted portions (10 ml) of the stock solution were added to 5-inch pyrex test tubes. The test tubes were protected by a calcium-chloride drying tube, cooled in a dry ice-acetone bath and sealed with a gas-oxygen flame. Each tube was placed in a thermostated oil bath at 95±0.01°C. After a measured time "t," the tube was removed and cooled in a dry ice-acetone bath. The tubes were opened and the liberated acid was titrated with 0.004852 N sodium hydroxide using a phenolphthalein indicator.

For the rate at 35°C, the solution was prepared at 35°C by immersing the weighed quantity of the (1-hydroxycyclohexyl)methyl tosylate and the aqueous ethanol mixture separately in the thermostated oil bath before mixing. After mixing, the entire stock solution was placed in the thermostated oil bath and after a measured time "t," 10 ml of the solution was pipetted into a conical flask. This was then titrated with 0.004852 N sodium hydroxide, using a phenolphthalein indicator. A blank titration of 1.2 ml was obtained.

The first order rate constants were calculated from the equation

$$k_1 = \frac{2.303}{t} \log \frac{a}{a-x} \tag{23}$$

This was done by plotting log(a-x) vs. time t, where 'a' is the initial concentration of (1-hydroxycyclohexyl)methyl tosylate and x is the decrease in its concentration after time t, as calculated from the titration. Straight lines were obtained with slopes equal to $-k_1/2.303$, where k_1 is the first order rate constant. The plots are shown in Figures 4 and 5. The rate constants at 95°C and 35°C are 1.59×10^{-3} sec^{-1} and 2.60×10^{-6} sec^{-1} respectively.

Reaction Products

In a 50-ml round-bottom flask was placed 0.2850 g (0.0101 mol.) of the tosylate. The flask was attached to an efficient condenser and equipped with a magnetic stirrer. To it distilled water (20 ml) was added, and the mixture was refluxed for one hour while stirring. The tosylate dissolved immediately when heated.

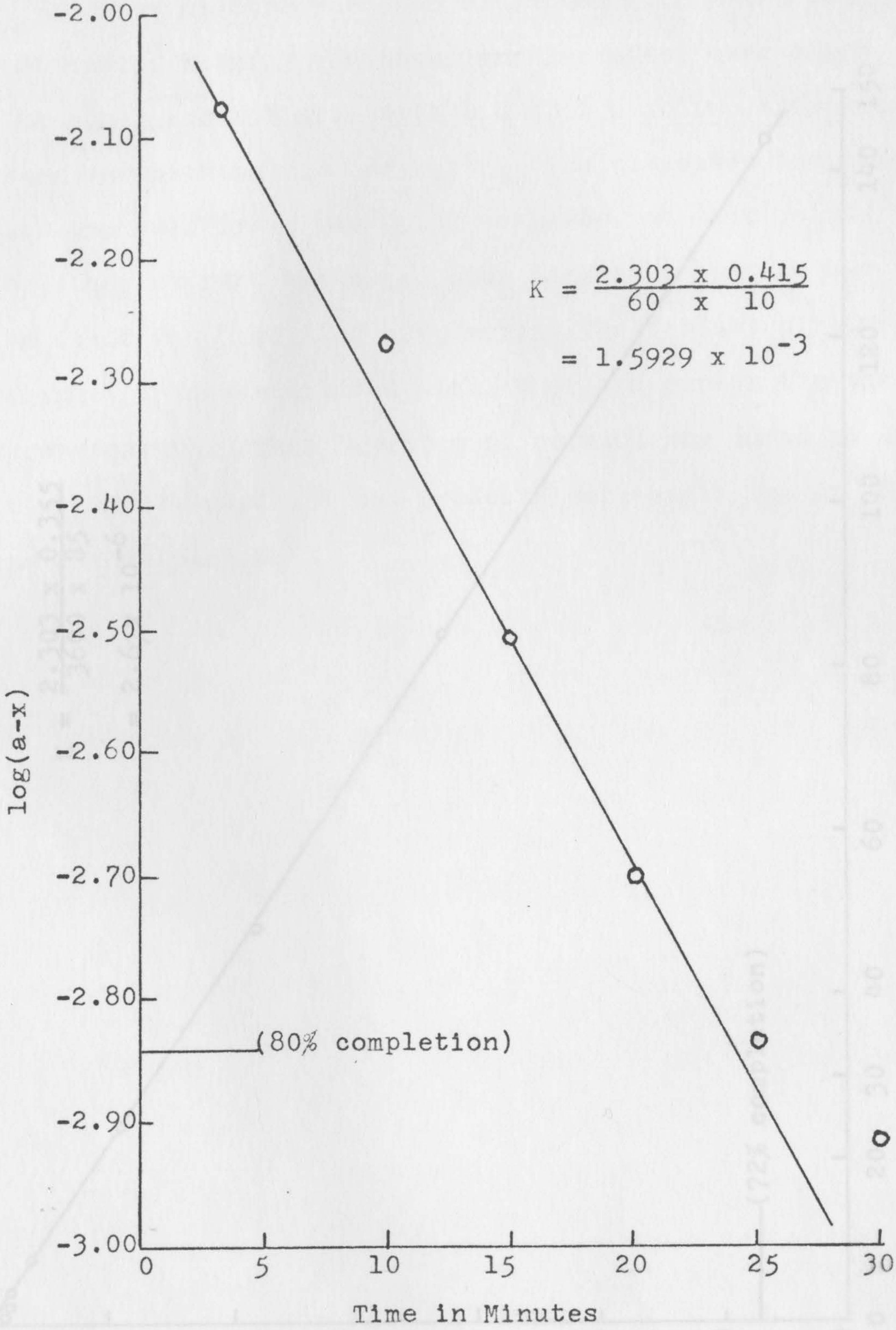


Fig. 4. Solvolysis of (1-Hydroxycyclohexyl)-methyl p-toluenesulfonate in 50% EtOH at 95°C.

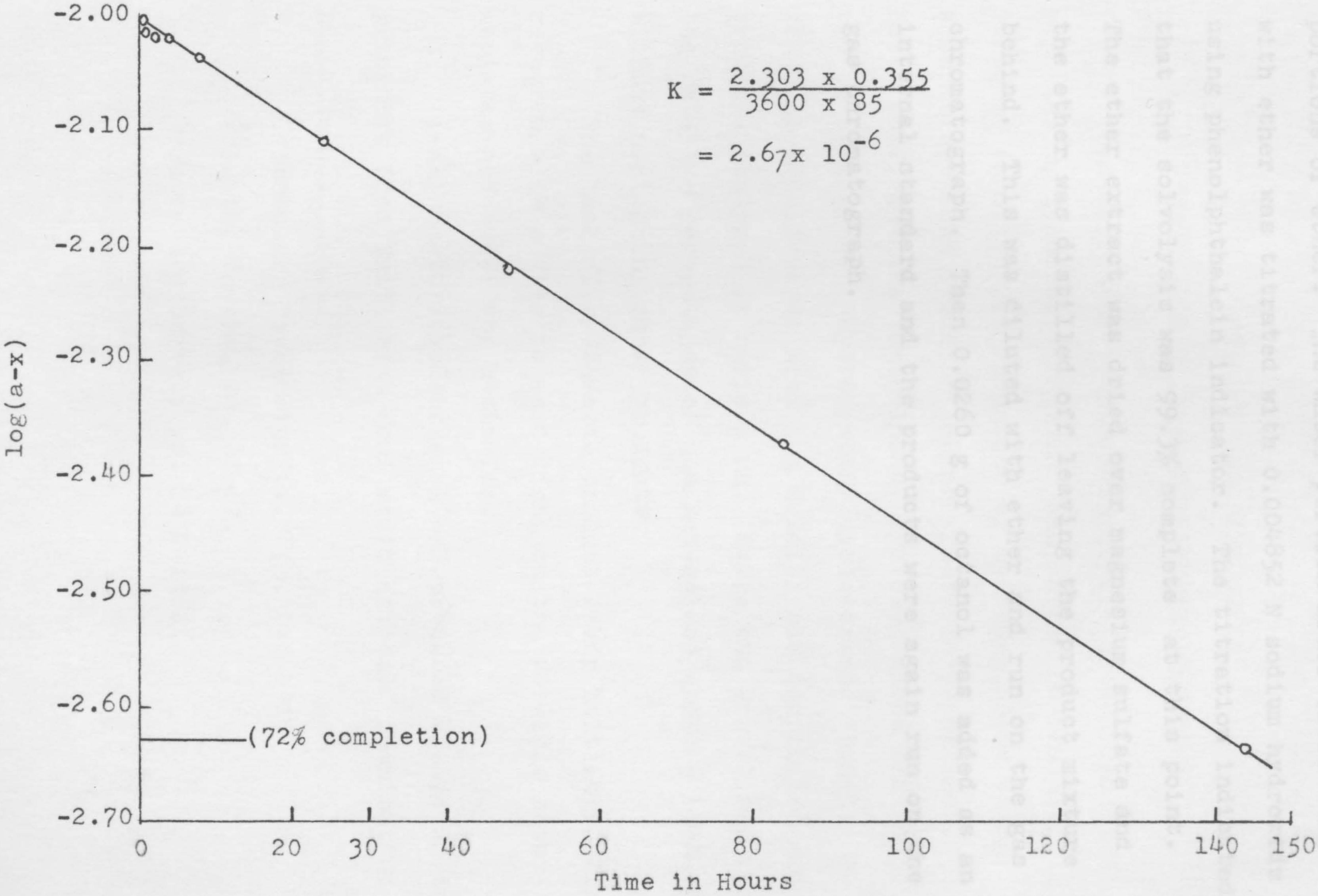


Fig. 5. Solvolysis of (1-Hydroxycyclohexyl)methyl p-toluenesulfonate in 50% EtOH at 35°C. log(a-x) vs. Time.

The mixture was then extracted with seven 10-ml portions of ether. The water portion after extracting with ether was titrated with 0.004852 N sodium hydroxide using phenolphthalein indicator. The titration indicated that the solvolysis was 99.3% complete at this point. The ether extract was dried over magnesium sulfate and the ether was distilled off leaving the product mixture behind. This was diluted with ether and run on the gas chromatograph. Then 0.0260 g of octanol was added as an internal standard and the products were again run on the gas chromatograph.

CHAPTER IV

RESULTS AND DISCUSSION

Deamination of 1-Aminomethylcyclohexanol

Deamination of 1-aminomethylcyclohexanol has been reported by Tchoubar,[49] Smith[50] and Favre and Gravel.[51] Tchoubar reported the formation of cycloheptanone along with an unstated yield of 1-hydroxymethylcyclohexanol. Smith confirmed the formation of cycloheptanone and reported the percentage of 1-hydroxymethylcyclohexanol formed. He found no epoxide even when the acidity was controlled and products analyzed at various pH. Favre and Gravel reported the relative percentages of the ketone and epoxide products without mentioning other products.

The lack of systematic product study initiated this research with a view to shed light on the possible intermediates and hence the mechanism.

1-Aminomethylcyclohexanol was prepared according to procedure from Smith with some modification. Deamination

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[49] Tchoubar, "Extension...," pp. 160-172.

[50] Smith, Thesis, pp. 42-62.

[51] Favre and Gravel, pp. 1452-1462.

was carried out in dilute aqueous phosphoric acid. A typical deamination is described in the experimental section.

The products isolated from the deamination of 1-aminomethylcyclohexanol were cyclohexanone (I), 1-oxaspiro(2,5)octane (II), cycloheptanone (III), cyclohexanecarboxaldehyde (IV), and 1-hydroxymethylcyclohexanol (V) along with three unidentified high boiling products (VI), (VII) and (VIII). Table 6 lists the overall yield of the products and Table 7 lists the percentage yields of the identified products on an absolute basis. The relative yield of each identified product as compared on a molar basis to all identified products is shown in Table 8.

TABLE 6

YIELDS OF ALL PRODUCTS FROM DEAMINATION OF 1-AMINOMETHYLCYCLOHEXANOL

Compound	Run 1		Run 2	
	Yield, g	Retention time, min	Yield, g	Retention time, min
I	0.00141	2.85	0.00045	2.80
II	0.00098	3.70	0.00044	3.80
III	0.07575	5.45	0.05643	5.40
IV	0.00220	6.50	0.00033	6.50
V	0.00068	9.60	0.00039	9.60
VI	0.01892	11.70	0.01101	11.70
VII	0.00198	26.40	0.00094	26.40
VIII	0.00775	28.70	0.00914	28.70

TABLE 7

OVERALL YIELDS OF THE IDENTIFIED PRODUCTS FROM 1-AMINOMETHYLCYCLOHEXANOL

Run	Compounds, % Yield					
	I	II	III	IV	V	Total
1	1.135	0.691	53.595	1.557	11.532	68.510
2	0.256	0.291	31.342	0.056	4.443	36.316

TABLE 8

RELATIVE YIELDS OF THE IDENTIFIED PRODUCTS FROM 1-AMINOMETHYLCYCLOHEXANOL

Run	Compounds, % Relative Yield					
	I	II	III	IV	V	Total
1	1.657	1.008	78.232	2.271	16.833	100.00
2	0.768	0.658	83.963	0.496	14.234	100.00

Our finding of about 1% cyclohexanone confirms the report by Favre and Gravel.[52] This product apparently resulted from the breakdown of the diazonium intermediate into diazomethane and cyclohexanone. Evidence of the formation of diazomethane in such systems was reported by Favre and Gravel in their studies of <u>trans</u> and <u>cis</u>-<u>tert</u>-butyl-4-aminomethyl-1-cyclohexanol and 1-aminomethylcyclohexanol, which gave 4-<u>t</u>-butyl-cyclohexanone in 1.5 to 5% yields.

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[52] Favre and Gravel, pp. 1452-1462.

The formation of diazomethane was also noted by English and Bliss[53] in the deamination of aliphatic 1,3-aminoalcohols and by Fessenden and Freenor[54] in the deamination of aminomethyltrimethylsilane. Since diazomethane is a comparatively stable neutral molecule, its formation would probably not require much energy. Also, a factor favoring such formation is the stability of the protonated ketone formed by the loss of diazomethane. It is well known that diazomethane is highly reactive and it could react with the ketone or aldehyde formed in the deamination to give epoxides and various other products.[55] The formation of diazomethane and subsequent reactions are outlined in equations 24 to 28. The possible products formed include 1-oxaspiro(2,6)nonane, cyclohexylmethylether, etc., and could possibly account for one or more of the unknowns observed in our results. However, no check has been made for these products.

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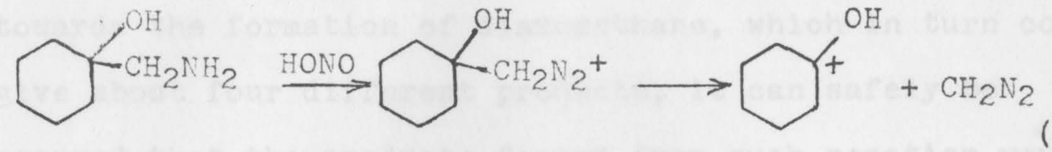
[53] J. English Jr. and A. D. Bliss, "The Preparation and Deamination of Some 1,3-Aminoalcohols," Journal of American Chemical Society, LXXVIII (1956), pp. 4057-4060.

[54] R. Fessenden and F. J. Freenor, "The Reaction of Aminotrimethylsilane with Nitrous Acid," Journal of Organic Chemistry, XXVI (1961), pp. 1681-1682.

[55] I. L. Finar, Organic Chemistry, Vol. 1, 5th ed. (London: The English Language Book Society and Longmans Green and Co., Ltd., 1969), p. 358.



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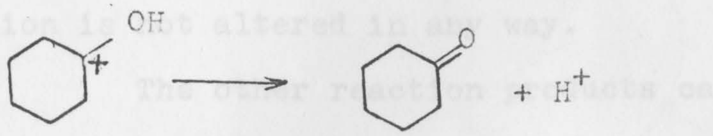

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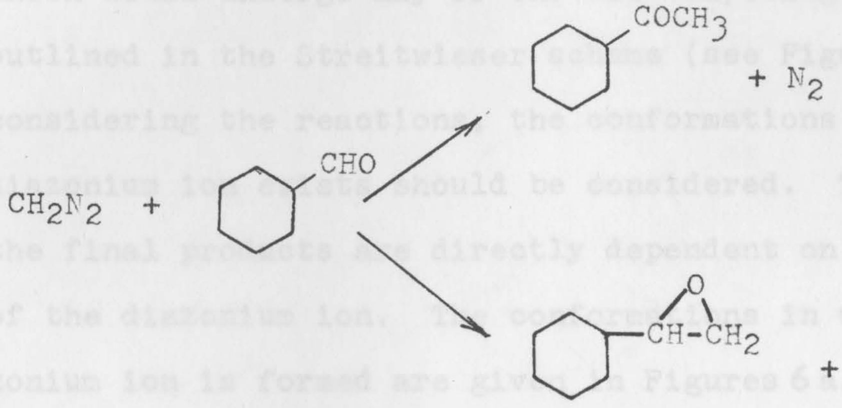
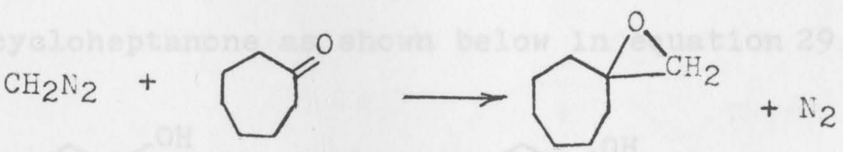


(26)



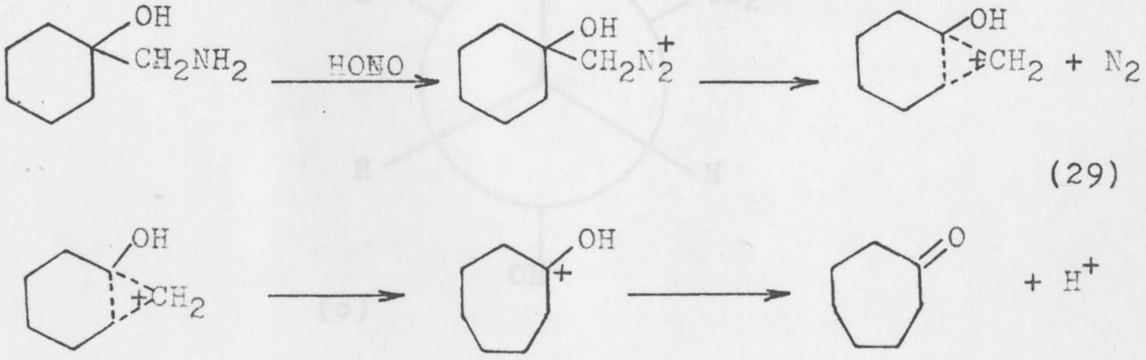
(27)

$CH_2N_2 + HCl \longrightarrow CH_3Cl + N_2$ (28)

Since only 1% cyclohexanone is formed and it essentially implies that only 1% of the reaction has gone towards the formation of diazomethane, which in turn could give about four different products, it can safely be assumed that the products formed from such reaction would be very small in quantity and that the course of the reaction is not altered in any way.

The other reaction products can be explained on the basis of the Streitwieser deamination scheme. It is recognized that a diazonium ion is formed as an intermediate which would undergo any of the six competing reactions outlined in the Streitwieser scheme (see Figure 2). Before considering the reactions, the conformations in which the diazonium ion exists should be considered. This is because the final products are directly dependent on the conformation of the diazonium ion. The conformations in which the diazonium ion is formed are given in Figures 6 a, b, and c.

The formation of cycloheptanone in larger quantity can be expected because conformations 6 a and 6 b would give cycloheptanone as shown below in equation 29.



(29)

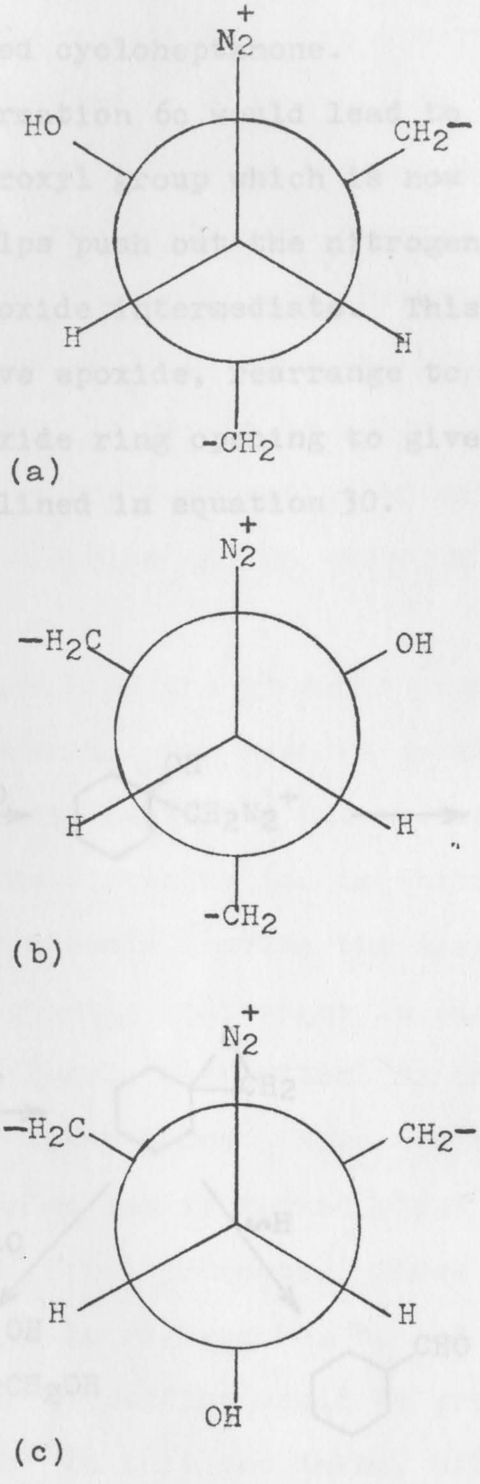
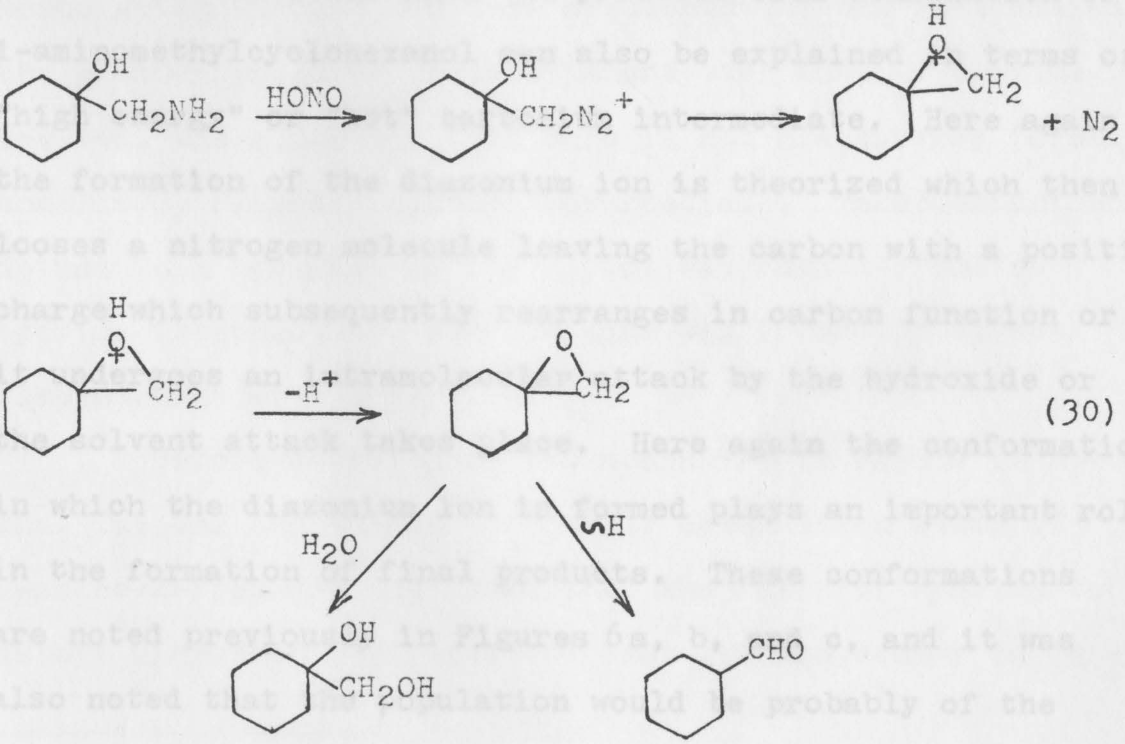


Fig. 6. Conformations of Diazonium Intermediates

The $-CH_2$ group which is in the favored trans position helps push out the nitrogen molecule forming a bridged methylene intermediate (or transition state) which rearranges to form the protonated cycloheptanone.

The conformation 6c would lead to the protonated epoxide. The hydroxyl group which is now in the favored trans position helps push out the nitrogen molecule to give the protonated epoxide intermediate. This would further deprotonate to give epoxide, rearrange to give aldehyde or would undergo epoxide ring opening to give glycol. The reactions are outlined in equation 30.



(30)

Since the reaction is carried out in an acidic medium the epoxide could deprotonate and reprotonate in continuous equilibrium and hence would tend to give more of the glycol than the epoxide as is observed.

It would further be expected that the order of population would be 6a = 6b > 6c because the conformation 4a and 4b would be sterically more favored to 6c. Thus the ratio of cycloheptanone to the products formed from the epoxide intermediate would be more than 2:1. The observed ratio is nearly 4:1. It should be noted that according to this given scheme the deamination of aminoalcohol proceeds through S_N2 - E2 mechanism and no unrearranged carbonium ion is formed.

On the other hand the products from deamination of 1-aminomethylcyclohexanol can also be explained in terms of "high energy" or "hot" carbonium intermediate. Here again the formation of the diazonium ion is theorized which then looses a nitrogen molecule leaving the carbon with a positive charge which subsequently rearranges in carbon function or it undergoes an intramolecular attack by the hydroxide or the solvent attack takes place. Here again the conformations in which the diazonium ion is formed plays an important role in the formation of final products. These conformations are noted previously in Figures 6a, b, and c, and it was also noted that the population would be probably of the order 6a = 6b > 6c. In this mechanism, nitrogen molecule is not pushed out. The diazonium molecule breaks down into a "high energy" carbonium ion and very stable nitrogen molecule. Thus in deamination of 1-aminomethylcyclohexanol the diazonium ion formed decomposes further to give the carbonium shown in Figure 7. This carbonium ion may react with the water to give glycol, or it may undergo carbon function rearrangement to give cycloheptanone with a subsequent loss of proton. The hydroxide group may attack to give the protonated epoxide which would then give epoxide or rearrange with a 1,2 hydride shift to give the aldehyde. Besides all these, an S_N2 type displacement of N_2 may take place before the decomposition occurs. This would again lead to the formation of 1-hydroxymethylcyclohexanol. As mentioned previously the amount of final products formed depend on conformation in which the diazonium ion is present, hence going through the same arguments one can rationalize the greater yield of cycloheptanone over that of epoxide. However, the glycol in this case is not necessarily formed completely from the epoxide intermediate. These experiments do not tell how much of the glycol was formed from the epoxide intermediate, and how much was formed by direct displacement with water.

Before deciding on the mechanism it should be noted that Tatsumi and Kotani[56] in their deamination study of 1-amino-2-propanol had found that the ratio of hydride to methyl migration was 1.5:1 and that intramolecular to inter-

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[56] Tatsumi and Kotani, pp. 1-9

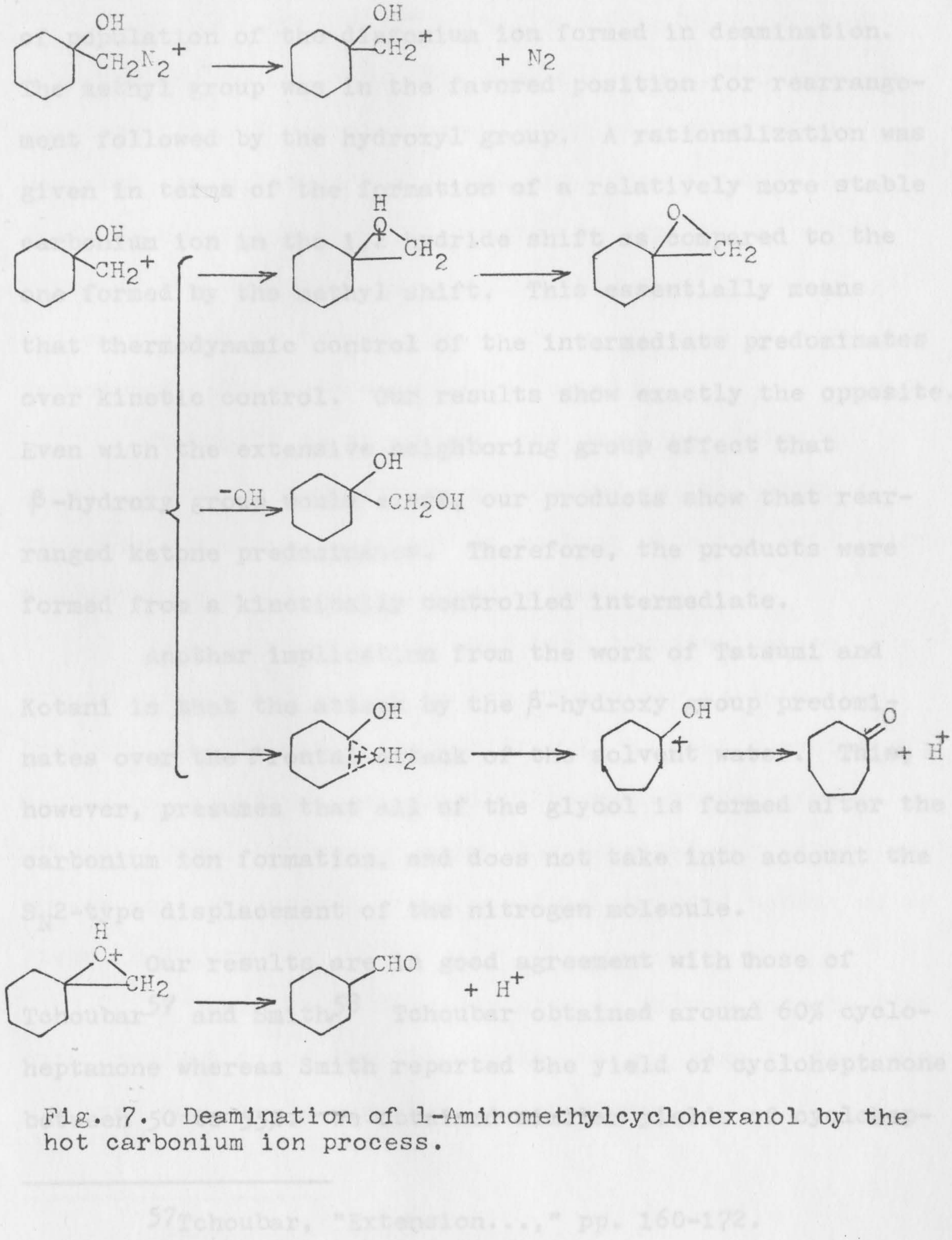

Fig. 7. Deamination of 1-Aminomethylcyclohexanol by the hot carbonium ion process.

molecular substitution was 1.8:1. The hydride to methyl migration ratio of 1.5:1 was not in accord with the order of population of the diazonium ion formed in deamination. The methyl group was in the favored position for rearrangement followed by the hydroxyl group. A rationalization was given in terms of the formation of a relatively more stable carbonium ion in the 1,2 hydride shift as compared to the one formed by the methyl shift. This essentially means that thermodynamic control of the intermediate predominates over kinetic control. Our results show exactly the opposite. Even with the extensive neighboring group effect that β-hydroxy group would exert, our products show that rearranged ketone predominates. Therefore, the products were formed from a kinetically controlled intermediate.

Another implication from the work of Tatsumi and Kotani is that the attack by the β-hydroxy group predominates over the frontal attack of the solvent water. This, however, presumes that all of the glycol is formed after the carbonium ion formation, and does not take into account the S_N2-type displacement of the nitrogen molecule.

Our results are in good agreement with those of Tchoubar[57] and Smith.[58] Tchoubar obtained around 60% cycloheptanone whereas Smith reported the yield of cycloheptanone between 50 to 55%. We obtained similar yields of cyclohep-

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[57] Tchoubar, "Extension...," pp. 160-172.

[58] Smith, Thesis. pp. 42-62.

tanone. Smith reported a 6-12% yield of 1-hydroxymethylcyclohexanol which is also in agreement with our results.

Favre and Gravel[59] in their deamination studies reported the formation of 80% cycloheptanone, 20% epoxide and less than 1% cyclohexanone. They have apparently reported the relative yields and have included all the products resulting from the epoxide intermediate in the reported 20% epoxide. Our results show that around 81.1% cycloheptanone is formed, 17.7% of the epoxide products are formed and 1.2% cyclohexanone is formed.

It should be noted that the relative yields of glycol, aldehyde and epoxide may depend on the length of time these products are left in contact with the acid, since the products may tend to co-equilibrate.

In view of the fact that both the Streitwieser scheme and the hot carbonium ion scheme can explain the products equally well, it is difficult to make a choice of mechanism. However, recognizing the neighboring group effect of the β-hydroxyl group, the Streitwieser scheme would appear more reasonable. The complete proposed mechanism is given in Figure 8.

It would be of interest at some future date to find out the identity of the three unknowns and also to seek some evidence for the formation of diazomethane.

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[59] Favre and Gravel, p.1452.

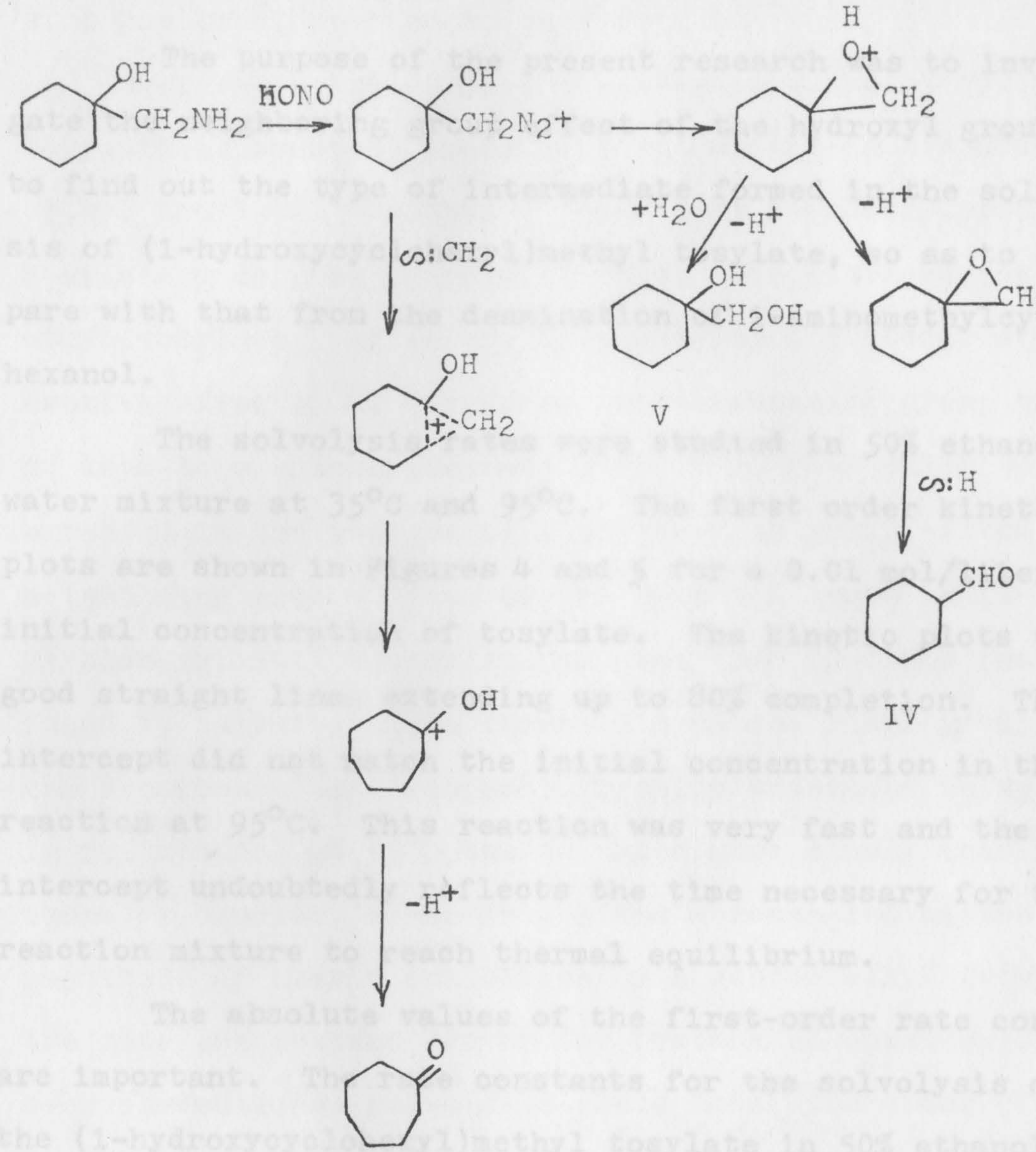

Fig. 8. Proposed mechanism of the 1-Aminomethylcyclohexanol deamination.

Solvolysis of (1-Hydroxycyclohexyl)-methyl p-Toluenesulfonate

The purpose of the present research was to investigate the neighboring group effect of the hydroxyl group and to find out the type of intermediate formed in the solvolysis of (1-hydroxycyclohexyl)methyl tosylate, so as to compare with that from the deamination of 1-aminomethylcyclohexanol.

The solvolysis rates were studied in 50% ethanol-water mixture at 35°C and 95°C. The first order kinetic plots are shown in Figures 4 and 5 for a 0.01 mol/liter initial concentration of tosylate. The kinetic plots were good straight lines extending up to 80% completion. The intercept did not match the initial concentration in the reaction at 95°C. This reaction was very fast and the intercept undoubtedly reflects the time necessary for the reaction mixture to reach thermal equilibrium.

The absolute values of the first-order rate constants are important. The rate constants for the solvolysis of the (1-hydroxycyclohexyl)methyl tosylate in 50% ethanol at 95°C was 1.59×10^{-3} sec^{-1} (Figure 4) and in 50% ethanol at 35°C was 2.60×10^{-6} sec^{-1} (Figure 5). The solvolysis rate of cyclohexyl p-toluenesulfonate in 50% ethanol at 40°C has been reported to be 5.30×10^{-5} sec^{-1}.[60] The solvolysis

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[60] Roberts, "Hydroxyl Group...," pp. 118-123.

rate of trans 2-hydroxycyclohexyl tosylate in 50% ethanol at 40°C has been reported to be 2.00×10^{-5}.[61]

Thus the solvolysis of (1-hydroxylcyclohexyl)methyl tosylate is about 19 times as fast as that of 2-hydroxypropyl tosylate. Kalthia[62] found that 2-hydroxylpropyl tosylate undergoes hydrolysis about four times as fast as ethyl tosylate. After proper allowance for steric and inductive effects, he estimated the neighboring group effect to lead to a solvolysis rate 3000 times that which would be expected in the absence of a neighboring group effect. The neighboring group effect of the hydroxyl group in (1-hydroxycyclohexyl)methyl tosylate is more than 19 times that found by Kalthia, since there is a second alkyl group at the β-carbon atom. Neopentyl bromide undergoes solvolysis in 50% ethanol at 95°C twelve times more slowly than does isobutyl bromide,[63] and this gives a rough indication of the magnitude of steric inhibition by a second alkyl group. Thus the rate enhancement factor for protonated epoxide formation over conventional solvolysis would be of the order of 19 x 12 x 3000 = 684,000. The arguments presented above are similar to those advanced by Winstein[64] to show the magnitude of the neighboring group effect in 2-methyl-2-methoxy-

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[61] Roberts, "Hydroxyl Group...," pp. 118-123.

[62] Kalthia, Thesis, pp. 1-63.

[63] A. Streitwieser Jr., Solvolytic Displacement Reactions (New York: McGraw-Hill Book Company, Inc., 1962) p.73.

[64] Winstein and Grunwald, p. 828.

1-propyl-p-bromobenzenesulfonate. Excessive reliance should not be placed on the actual number shown, but the argument serves to show that the neighboring group effect is large. Possibly this large effect may be caused by greater relief of steric strain in the transition state for epoxide formation in the more highly substituted cyclohexane derivative. At any rate, it is clear that the intermediate must be a protonated epoxide.

A similar but less pronounced rate enhancement by the β-hydroxyl group has also been shown by Roberts[65] in his solvolysis study of cyclic aliphatic tosylates and hydroxy tosylates.

For product study the tosylate was solvolyzed in pure water as shown in experimental section, and the products were analyzed by vapor phase chromatography. The products obtained from the solvolysis of (1-hydroxycyclohexyl)methyl tosylate along with their overall percent yield and relative percent yield are listed in Table 9. The products were identified and absolute yields were determined by gas chromatography using octanol as the internal standard. The products as seen from Table 9 are 1-oxaspiro(2,5)octane, cyclohexanecarboxaldehyde and 1-hydroxymethylcyclohexanol. The total overall yield was around 48.5%.

These products may be explained on the basis of the following proposed mechanism in Figure 9.

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[65] Roberts, "Hydroxyl Group...," p. 118.

TABLE 9

PRODUCTS FROM THE SOLVOLYSIS OF (1-HYDROXYCYCLOHEXYL)METHYL TOSYLATE

Compound	Yields in g			Overall % Yield			Relative % Yield		
	Run 1	Run 2	Run 3	Run 1	Run 2	Run 3	Run 1	Run 2	Run 3
1-Oxaspiro(2,5)-octane	0.01233	0.01193	0.01226	11.00	10.63	10.93	22.71	22.11	22.20
Cyclohexanecarboxaldehyde	0.00847	0.00786	0.00856	7.55	7.01	7.63	15.59	14.58	15.50
1-Hydroxymethylcyclohexanol	0.03890	0.03962	0.03994	29.88	30.43	30.67	61.70	63.30	62.30

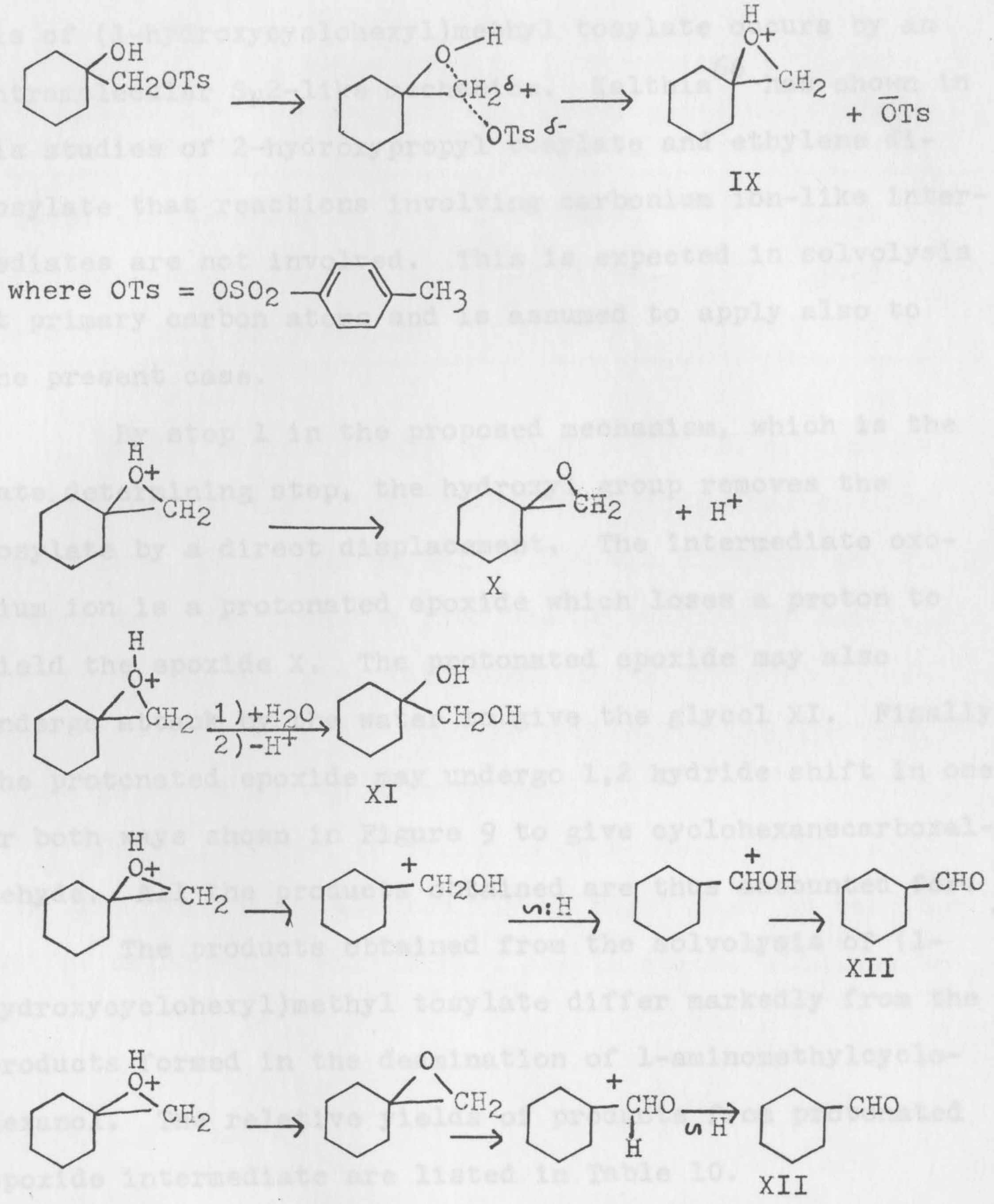

Fig. 9. Proposed Mechanisms for the Solvolysis of (1-Hydroxycyclohexyl)methyl Tosylate

The mechanism proposed indicates that the solvolysis of (1-hydroxycyclohexyl)methyl tosylate occurs by an intramolecular S_N2-like mechanism. Kalthia[66] has shown in his studies of 2-hydroxypropyl tosylate and ethylene ditosylate that reactions involving carbonium ion-like intermediates are not involved. This is expected in solvolysis at primary carbon atoms and is assumed to apply also to the present case.

By step 1 in the proposed mechanism, which is the rate determining step, the hydroxyl group removes the tosylate by a direct displacement. The intermediate oxonium ion is a protonated epoxide which loses a proton to yield the epoxide X. The protonated epoxide may also undergo attack by the water to give the glycol XI. Finally the protonated epoxide may undergo 1,2 hydride shift in one or both ways shown in Figure 9 to give cyclohexanecarboxaldehyde. All the products obtained are thus accounted for.

The products obtained from the solvolysis of (1-hydroxycyclohexyl)methyl tosylate differ markedly from the products formed in the deamination of 1-aminomethylcyclohexanol. The relative yields of products from protonated epoxide intermediate are listed in Table 10.

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[66] Kalthia, Thesis, pp. 1-63.

TABLE 10

RELATIVE YIELDS OF PRODUCTS FROM PROTONATED EPOXIDE INTERMEDIATE

Products	Deamination	Solvolysis
1-Oxaspiro(2,5)octane	4.75	22.34
Cyclohexanecarboxaldehyde	7.89	15.22
1-Hydroxymethylcyclohexanol	88.51	62.43

Of the approximately 5% absolute yield of deamination products assumed to be based on a protonated epoxide intermediate, 88.5% was glycol, 7.89% was aldehyde and 4.75% was epoxide. The products from the solvolysis of tosylate were around 22% epoxide, 16% aldehyde and 62% glycol. It should, however, be noted that in both cases the protonated epoxide is shown as the intermediate.

The difference in relative percentage of the products from protonated epoxide may be attributed to the fact that the deamination was carried out in strong acid medium.

BIBLIOGRAPHY

Books

Banthorpe, D. V. "Rearrangements Involving Amino Groups." The Chemistry of the Amino Group. Edited by Saul Patai. New York: Interscience Publishers, Inc., 1968.

Dictionary of Organic Compounds. Volume 2, fourth edition. Edited by G. Harris. New York: Oxford University Press, 1965.

Eliel, E. L. and Freeman, J. P. Organic Syntheses. Vol. 33. Edited by Charles C. Price. New York: John Wiley and Sons, Inc., 1953.

Finar, I. L. Organic Chemistry. Vol. 1, fifth edition. London: The English Language Book Society and Longmans Green and Co., Ltd., 1969.

Friedman, Lester. "Carbonium Ion Formation from Diazonium Ions," Carbonium Ions. Volume II. Edited by George A. Olah and Paul von R. Schleyer. New York: Wiley-Interscience, 1970.

Kosower, E. M. An Introduction to Physical Organic Chemistry. New York: John Wiley and Sons, Inc., 1968.

Morrison, R. T. and Boyd, R. N. Organic Chemistry. Second edition. Boston: Allyn and Bacon, Inc., 1966.

Noller, C. R. Chemistry of Organic Compounds. Third edition. Philadelphia: W. B. Saunders Company, 1965.

Pocker, Y. "Wagner-Meerwin Pinacolic Rearrangements in Acyclic and Cyclic Systems," Molecular Rearrangements: Part I. Edited by Paul DeMayo. New York: Interscience Publishers, 1963.

Streitwieser, Andrew Jr. Solvolytic Displacement Reactions. New York: McGraw-Hill Book Company, Inc., 1962.

Zollinger, H. Azo and Diazo Chemistry. New York: Interscience Publishers, 1961.

Articles

Bachmann, W. E. and Moser, F. H. "The Pinacol-Pinacolin Rearrangement. The Relative Aptitudes of Aryl Groups," Journal of American Chemical Society, LIV (1932) 1124-1133.

Bailey, P. S. and Burr, J. G. Jr. "Evidence for a Cyclic Intermediate in the Reaction of Diarylethylamines with Nitrous Acid," Journal of American Chemical Society, LXXV (1953) 2951-2955.

Carlson, R. G. and Behn, N. S. "Ring Expansions I. Ring Expansion of the Epimeric *trans*-2-Aminomethyl-2-decalols and *trans*-2-Decalone," The Journal of Organic Chemistry, XXXIII (1968) 2069-2072.

Ciereszko, L. S. and Burr, J. G. Jr. "Migration Ratios Observed in the Reaction of Diarylethylamines with Nitrous Acid," Journal of American Chemical Society, LXXIV (1952) 5431-5433.

Corey, E. J. and Chaykovsky, M. "Dimethyloxosulfonium Methylide and Dimethylsulfonium Methylide. Formation and Application to Organic Synthesis," Journal of American Chemical Society, LXXXVII (1965) 1353-1364.

Curtin, D. Y. and Crew, M. C. "Migration Ratios in the Rearrangement of 2-Amino-1,1-diarylethanols," Journal of American Chemical Society, LXXVI (1954) 3719-3725

English, J. Jr. and Bliss, A. D. "The Preparation and Deamination of Some 1,3-Amino Alcohols," Journal of American Chemical Society, LXXVIII (1956) 4057-4060.

Favre, H. and Gravel, D. "Effets Stéréoélectroniques Dans La Désamination Nitreuse Des tert-Butyl-4-Aminométhyl-1-cyclohexanols cis Et trans," Canadian Journal of Chemistry, XLI (1963) 1452-1462.

Fessenden, R. and Freenor, F. J. "The Reaction of Aminomethyltrimethylsilane with Nitrous Acid," The Journal of Organic Chemistry, XXVI (1961) 1681-1682.

Kalthia, H. "The Solvolysis of Ethylene Di-tosylate and 2-Hydroxypropyl Tosylate," M.S. Thesis, Youngstown State University, 1970.

Ridd, J. H. "Nitrosation, Diazotization and Deamination," Quarterly Reviews (London), XV (1961) 418-441.

Roberts, D. D. "Neighboring Hydroxyl Group Effects in Solvolysis Reactions of Common Ring p-Toluenesulfonates," The Journal of Organic Chemistry, XXXIII (1968) 118-123.

Roberts, D. D. and Traynham, J. G. "A Solvolytic Investigation of Cyclooctyl and trans-2-Hydroxycyclooctyl Bromides and p-Toluenesulfonates," The Journal of Organic Chemistry, XXXII (1967) 3177-3182.

Smith, Bill B. "The Application of the Favorski Rearrangement to the Production of A-Norsteroids and the Preparation and Nitrous Acid Deamination of 1-Aminomethyl-cyclohexanol," Ph.D. Dissertation, Brown University (1953).

Streitwieser, Andrew Jr. "An Interpretation of the Reaction of Aliphatic Primary Amines with Nitrous Acid," The Journal of Organic Chemistry, XXII (1957) 861-869.

Tatsumi, C. and Kotani, R. "Rearrangement V. - Relative Migratory Aptitude in the Nitrous Acid Deamination of Some Aliphatic Aminoalcohols," Bulletin University Osaka Prefect, Ser. B, XIX (1967) 1-9.

Tchoubar, B. "Extension of Alicyclic Rings in 1(aminomethyl)-cycloalkanols by Nitrous Acid Deamination," Bulletin Societe Chimique De France, 216 (1949) 160-172.

Tchoubar, B., Weill, P. and Tiffeneau, M. "Isomerization of Methylenecyclohexane oxide to Hexahydrobenzaldehyde and Desamination of the Corresponding Aminoalchol to Cycloheptanone," Comptes Rendus, 205 (1937) 54-56.

Winstein, S., Lindegren, C. R. and Ingraham L. L. "Neighboring Carbon and Hydrogen. XV. Rearrangement as a Sequel to Neighboring Functional Group Participation. Solvolysis of 2-Methyl-2-methoxy-1-propyl p-Bromobenzenesulfonate," Journal of American Chemical Society, LXXV (1953) 155-158.

Winstein, S. and Grunwald, E. "The Role of Neighboring Groups in Replacement Reactions. XIII. General Theory of Neighboring Groups and Reactivity," Journal of American Chemical Society, LXX (1948) 828-837.