Dynamic Stereochemistry

Dynamic Stereochemistry:

An Insight into the 3D-Picture in the Course of a Reaction

By

Sudhir Chandra Pal

Cambridge Scholars Publishing

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To

my loving wife

ITIKA PAL (SAHA)

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FOREWORD

Often referred to as the chemistry in three-dimensions, stereochemistry is one of the most fascinating, as well as challenging subject. Ever since the landmark discovery of Louis Pasteur of the optical activity and chirality of tartaric acid, stereochemistry has become a pivotal subject, not only within organic chemistry but also in the broader fields of pharmaceuticals, materials science, biochemistry. This book on stereochemistry, titled "DYNAMIC STEREOCHEMISTRY" by Professor Sudhir Pal, who has vast experience in teaching stereochemistry to undergraduate students, comes out at a time when the need for a deeper understanding of spatial molecular arrangements has become so important. With the advent of new chiral drugs and advanced materials, it becomes increasingly important to grasp the concept of how molecular orientation and reactivity in 3D-space can drastically affect the outcome or stereoselectivity of a chemical reaction and the biological properties.

What sets this book apart from the rest of already published ones, is the rigorous exploration of reactivity of molecules in motion in 3D-space with other molecules, reagents or biomolecules and its effect on asymmetric synthesis. The author has managed to balance the depth of the subject matter with clarity, guiding both students and experienced chemists through the fundamental concepts of kinetics of asymmetric chemical reactions.

It is my sincere belief that this book will become an essential reference for anyone seeking to navigate through the world of inter-reactivity of three-dimensional molecular structures. The chapters are very well organised with the unravelling of topics in a pedagogical manner. The problems at the end of each chapter will help the readers to boost up their understanding of 3D-chirality.

My congratulations to Professor Pal for this outstanding effort. I believe this book will be regarded as a stepping stone to the broader and dynamic portrait of how molecules shape the chiral world around us.

Amit Basak, FNA, FRSC, FASc, FNASc
INSA Senior Scientist, IISER Kolkata
Formerly Professor, Head (Chemistry) and Dean (Faculty)
Indian Institute of Technology Kharagpur, INDIA

PREFACE

The book discusses the application of the basic aspects / principles of stereochemistry in organic reactions. It correlates the stereochemistry of starting reactant and products in terms of the transition state and the intermediates.

Further, it deals with the studies of the effect of stereochemistry on the rate process – be it chemical reactions or conformational interconversions. The conformational theory provides a logical basis of these observations and also provides information regarding the relative reactivity of stereoisomers.

There are a number of literatures on the subject. But newer reactions and strategies for the synthetic methods are developed. The book attempts to highlight these topics in addition to presenting the existing reactions in a different approach.

A large number of problems are given in the exercise. Their solution is given for the benefit of the learners. Moreover, a good number of multiple-choice type questions are given to help the students in facing different competitive examinations. The book is made student-oriented.

The teaching and learning of this subject are the main purpose of the book. It is hoped that the students and teachers interested in this area will welcome the book.

I appreciate the assistance of Professor Samik Nanda (IIT, Kharagpur), Dr. Nirmal K Hazra (Egra S.S. Mavidyalaya), Dr. Subhabrata Mabhai (Mahishadal Raj College), Dr. Gopal Chandra Maity (Abhedananda Mahavidyalaya), for some helpful discussions and suggestions on some of the subject matters.

I take this opportunity to thank Prof. Alakes Bisoi (IISER, Kolkata), Prof. Prasanta Ghorai (IISER, Bhopal), Prof. Anirban Misra (NBU), Prof. Anirban Bhunia (Bose Institute), Prof. Snehadri Khatua (NEHU), Prof. Akhil K Sen (BIT, Mesra), Dr. Dipankar Das (US Pharmacopeia), Dr. Subir Roy (DRDO), Dr. Akbar Ali (ITC), Dr. Sankar P Dey (Principal), Dr.

Avishek Ghosh (Midnapore City College), Sri Debabrata Sarkar (Entrepreneur) and many others for their direct and indirect help.

I am grateful to all the teachers, especially Sri Bimal K Das and Late Jatindranath Paria, Prof. S. Bagchi and Prof. M. R. Jana, of my student life for their inspiration. I am also grateful to my research guide Prof. Avijit Banerji for arousing interest in the topic and organic chemistry in general.

I am indebted to my family members but for whose cooperation the work could not be done.

Finally, I take this opportunity to thank M/s Cambridge Scholars Publishing to publish the work in print and in electronic media

In spite of the best efforts, some errors may creep in. I shall appreciate and be grateful if learned readers bring these errors to the notice of the author. Their suggestions in improving the quality of the book in any respect are most welcome.

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CHAPTER 1

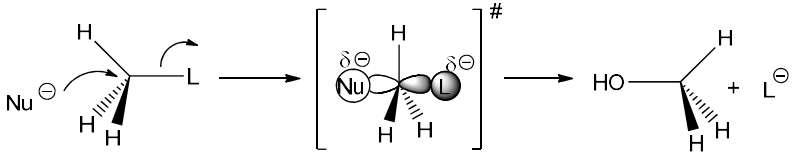
Nucleophilic Substitution at a Saturated C-Centre

1.1 Introduction

The two most common mechanism of the nucleophilic substitution at a saturated C-centre (sp^3 hybrid carbon) are (i) S_N2 (substitution, nucleophilic, bimolecular) and (ii) S_N1 (substitution, nucleophilic, unimolecular). Neighbouring group participation route and S_Ni are two other less common mechanisms.

1.2 S_N2 Mechanism

This is a concerted process (i.e, single step) in which the transition state (T. S.) is a penta-coordinated species (**Scheme 1.1**). The reaction centre changes its state of hybridisation to sp^2 in the T.S. such that its unhybrid p-orbital forms two partial bonds with the nucleophile (the incoming group, Nu) and the nucleofuge (the departing group, L). The situation demands that the nucleophile should approach the reaction centre from the rear side of the leaving group; the Nu…C…L is more or less linear.



Scheme 1.1

The characteristic features of S_N2 mechanism are supported by the following observations:

(i) *Kinetic studies*:

(a) the rate is second order – 1st order each with respect to the substrate and the reagent.[1] The energy profile diagram is shown in **Fig. 1.1a**.

(b) The rate of the S_N2 reactions gradually decrease from methyl to primary to secondary to tertiary substrates (**Fig. 1.2a**); the α-branching

raises the energy of the T. S. more than that of the ground state (**Fig. 1.1b**). This is because *the steric requirement of the T. S. [penta-coordinated] is higher than the steric requirement of the ground state [tetra-coordinated]* (**steric hindrance**).[1a]

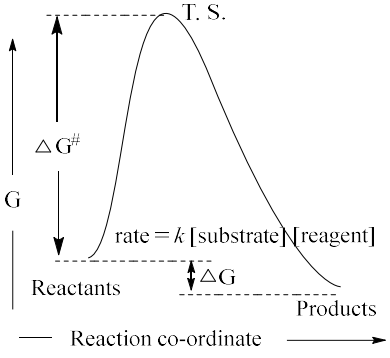


Fig. 1.1a

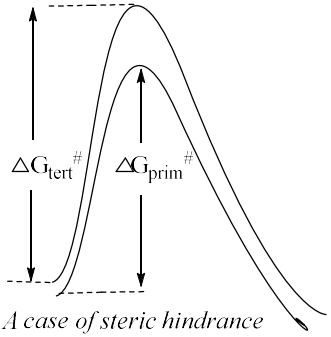


Fig. 1.1b

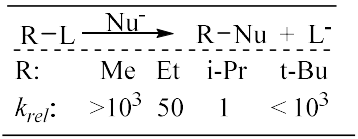


Fig. 1.2a

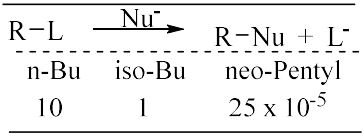
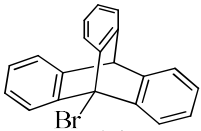


Fig. 1.2b

(ii) *Failure of the reactions at the bridgehead positions* - Even the reactions can fail if the situation so warrants. As for example the bridged compounds, (A), (B) and (C), with the leaving groups at the bridgehead positions, are inert towards the S_N2 reactions. The cage like framework totally blocks the rear side approach of the nucleophile.

(A)

(B)



(C)

[1]If the concentration of one reactant is made too high then its change in concentration would have no effect on the rate of reaction. The reaction is then called **pseudo first order** reaction though the mechanism is bimolecular.

[1a]see **Section 7.2** of 'Fundamentals of Stereochemistry' by the author.

(iii) The β-branching of the substrate also slows down the reaction (**Fig. 1.2b**). Then neopentyl substrates practically do not undergo the S_N2 reactions primarily due to the failure to attain collinearity, Nu…C…L, in the T.S. (**Fig. 1.3**). Such crowding of the rear side of the leaving group prohibiting collinearity is also the cause of the sluggishness of S_N2 reaction of the decalin derivative, (D).

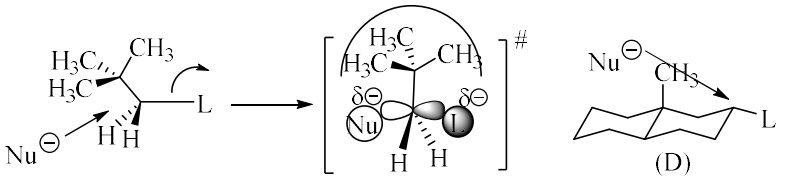
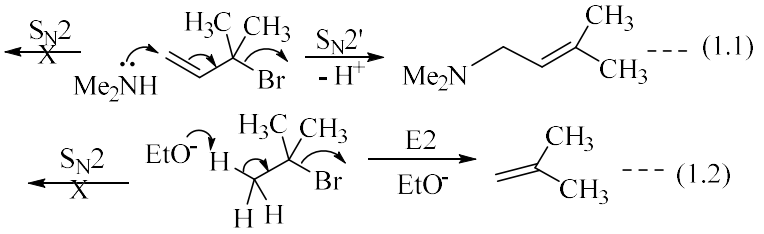


Fig. 1.3

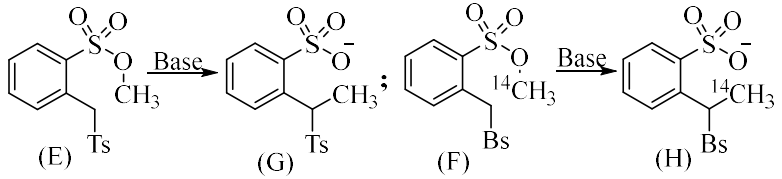
(iv) *The change of reaction course* - The reaction can take a different route if the access to the rear side of the leaving group is restricted or the S_N2 T.S. becomes crowded. Thus, even though the allylic substrates are more reactive towards substitution the compound, (E), gives mainly a rearranged product (by S_N2') under the bimolecular reaction condition (eqn. 1.1).

The percentage of elimination (by E2) increases from the primary to secondary to the tertiary substrates[2], and if the nucleophile is strongly basic the tertiary substrates give exclusive elimination product(s) (eqn. 1.2: failure of the Williamson synthesis).

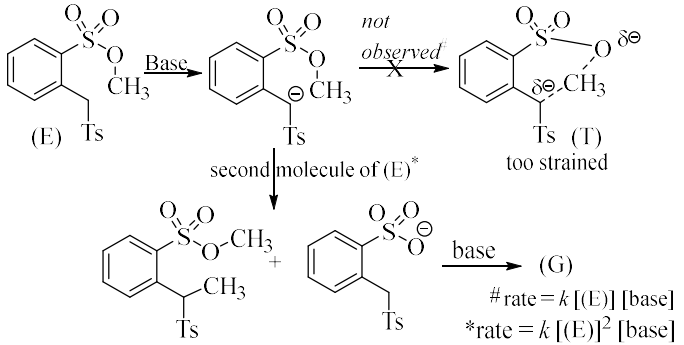


(v) *Failure of the intra-molecular reactions* - An expected intramolecular S_N2 reaction fails where the linearity, Nu…C…L, cannot be achieved due to any geometrical restriction (see also **Section 8.2**).

(a) Thus, the ortho-substituted sulfonic acid methyl esters (E) and (F) yield products (G) and (H) respectively by the intermolecular[3] rather than an intra-molecular process.



The kinetic studies indicate that the rate of each is second order in the substrate (intermolecular). The intra-molecular reaction[4] (1st order in substrate), despite favourable entropy factor, fails since the 6-membered T.S., (T), with the collinear arrangement of the three reacting centres in the already rigid framework of the benzenoid ring would be highly strained (**Scheme 1.2**).



Scheme 1.2

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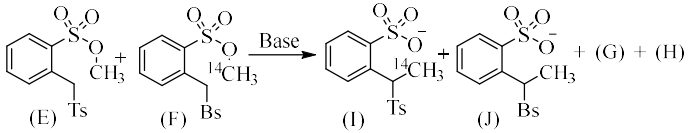
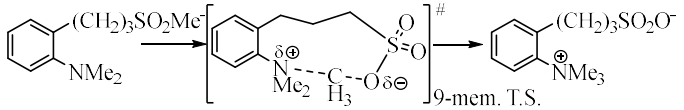
[2]The increased stability of the alkenes favouring the E2 T.S. and the statistical consideration of having a greater number of β-H are other causes for this trend.

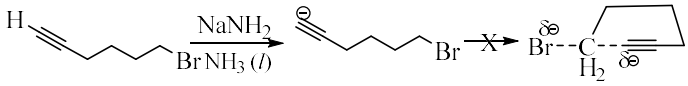
[3]The intermolecular path is established by the following cross-over experiment (this does not exclude simultaneous intra-molecular process). The intra-molecular path is excluded by the kinetic experiments.



[4]The intramolecular reaction (including cyclisation) could occur provided the ring of the T.S. is sufficiently large to allow collinearity of the participating centres.



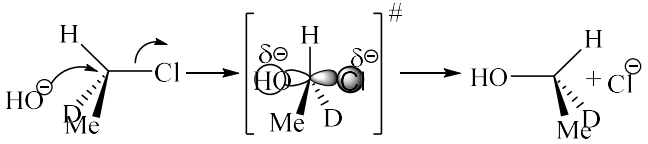
(b) The following reaction did not give the expected cyclic product; the 6-centre T.S. containing two sp-hybrid carbons (requiring linear geometry, too) would be too strained (**Scheme 1.3**).[5]



Scheme 1.3

(vi) **Stereochemical observations**: The inversion of configuration at the stereogenic reaction centre occurs; this is called **Walden inversion**.[6] As a result the following observations are noted:

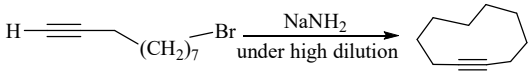
(a) the product from an enantiopure substrate having α-carbon as the only stereocentre is found to have the enantiomeric configuration of the starting isomer (**Scheme 1.4**).[7]



Scheme 1.4

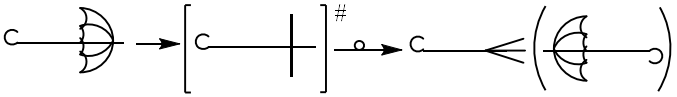
(b) the relative configuration of the diastereomeric starting compound (having stereogenic reaction centre, of course) is changed. That is, a threo-

[5] A longer chain can lead to an intramolecular reaction by S_N2:



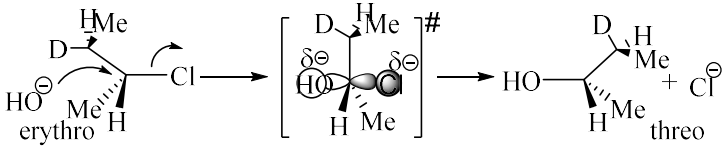
cyclodecyne

[6] The situation is analogous to the phenomenon of umbrella inversion in strong wind with the exception that here the umbrella gets 'folded'. Can anyone try to keep it 'unfolded' even in the inverted position (as shown in the parenthesis)? In that case analogy will be more appropriate (the umbrella will find a good market).



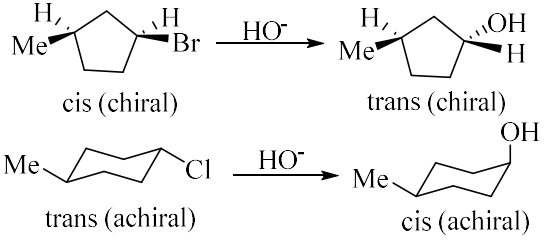
[7] This does not mean that configurational notation in terms of *R/S* would be changed. It is certainly changed if the priority of the leaving group in the starting isomer and the priority of the entered group in the product isomer is same. If the leaving group is written in place of the newly entered group in the product isomer the resultant would become the enantiomer of the starting isomer.

isomer forms an erythro product (meso in the limiting case) and *vice-versa* (**Scheme 1.5**).



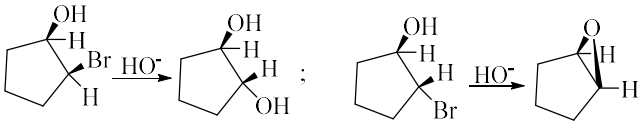
Scheme 1.5

In case of a cyclic substrate the cis-isomer (chiral / achiral) gives a trans-product (chiral / achiral) or the reverse (**Scheme 1.6**).



Scheme 1.6

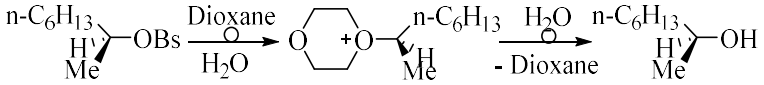
Cis-2-bromocylcopentanol undergoes a normal S_N2 reaction in the presence of a base (nucleophilic) to give a trans-diol. However, the corresponding trans-isomer, following an internal nucleophilic attack, yields an epoxide under the similar conditions (**Scheme 1.7**).



Scheme 1.7

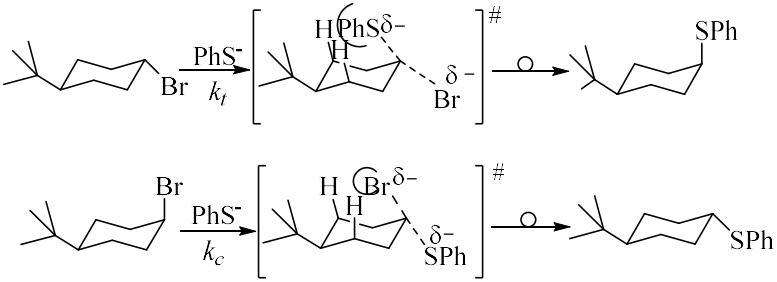
(c) Where the incoming and the leaving groups are same, the substitution at a stereocentre leads to the racemisation. The rate of the racemisation is twice the rate of reaction at the initial stages. This is shown by a reaction of an enantiopure iodo-compound labelled with a radioactive iodide (see **Section 7.4.2**). The experiment clearly indicates that each act of S_N2 reaction accompanies inversion of configuration at the reaction centre.

(d) Two S_N2 acts in a reaction mechanism can lead to a product with the retention of configuration. The solvolysis of an enantiopure starting compound (**Scheme 1.8**) in aqueous dioxan yielding a product with the retention of configuration is explained by an S_N2 involving nucleophilic solvent followed by another S_N2 step resulting in the final product.



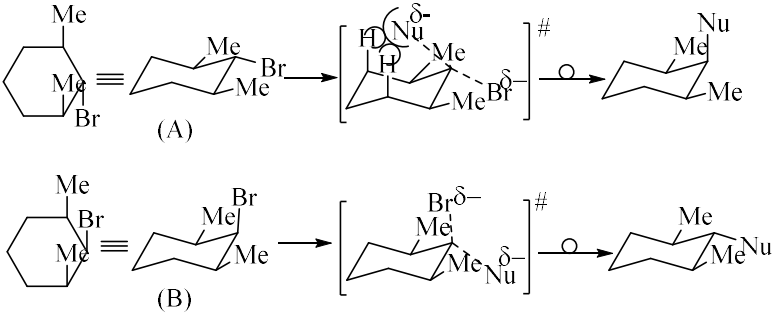
Scheme 1.8

(e) A bulky nucleophile (bulkier than the leaving group) prefers to enter along the equatorial rather than the axial path in the reaction with a cyclohexyl substrate. Thus, trans-4-tert-butylcyclohexyl bromide undergoes the reaction with thiophenolate at a slower rate than the corresponding cis-isomer ($k_t < k_c$: **Scheme 1.9**).



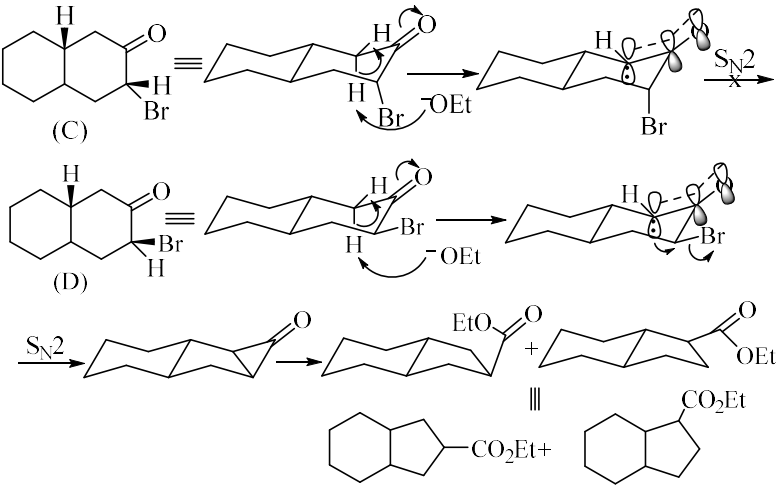
Scheme 1.9

Steric hindrance (see also **Section 7.2.2**) is responsible for the sluggish reaction of *r*-1-bromo-*t*-2, *t*-6-dimethylcyclohexane (A) as compared to the diastereomeric *r*-1-bromo-*c*-2, *c*-6-dimethylcyclohexane (B) with a nucleophile under bimolecular reaction condition. Both the isomers react through their biased conformers (A) and (B) in which both the methyl groups are equatorial. The incoming nucleophile faces crowding with the axial Hs at C-3 and C-5 in (A) to raise the energy of the T.S., and so the reaction rate is slow. The equatorial approach of the nucleophile in (B) does not face such steric situation (**Scheme 1.10**).



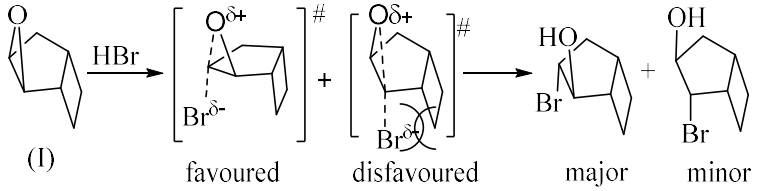
Scheme 1.10

(f) An intramolecular S_N2 is a primary step in the formation of a cyclopropanone intermediate in the Favorsky rearrangement. The failure to fulfil the stereoelectronic requirement of S_N2 to form such an intermediate is believed to be the cause of the unsuccessfulness of the Favorsky reaction of the α-bromoketone (C) where -Br is axial. Whereas the epimeric α-bromoketone (D) having the equatorial -Br undergoes the reaction to yield the ring contracted products (**Scheme 1.11**) as usual.

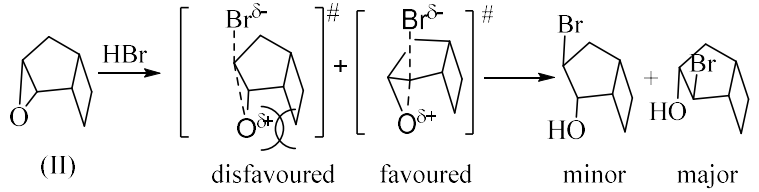


Scheme 1.11

(g) The steric factor sometimes influences the *regioselectivity* of the S_N2 reactions. The exo-epoxide (I) resists bromide attack at the carbon close to a 4-membered ring (**Scheme 1.12**), and the endo-epoxide (II) prevents -OH to develop at the carbon close to it (**Scheme 1.13**).



Scheme 1.12



Scheme 1.13

1.2.1 Allylic substrates: S_N2' mechanism and its stereochemistry –The probable mechanism and the stereochemical course for a chiral secondary substrate is depicted in **Fig. 1.3a**. Sometimes approach of the nucleophile is observed anti. but in most of the vinylogous S_N2' reactions the same approach is found to be syn / cis if the reactions are synchronous (Magid Fruchey, 1979*)*.

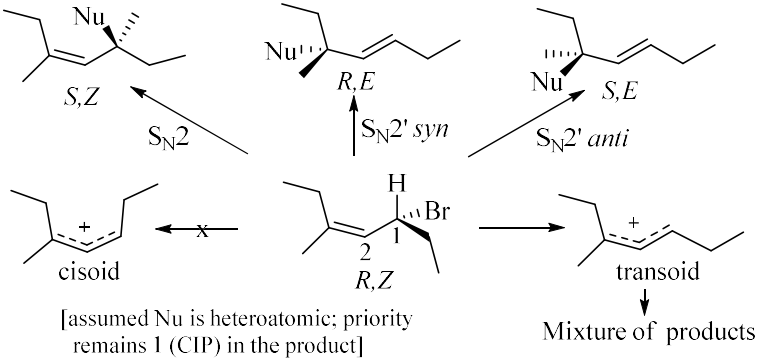


Fig. 1.3a

This stereochemistry is a natural consequence of (i) the trans-bending of an alkene upon interaction with a nucleophile, (ii) the preferred staggered arrangement of the allylic groups with respect to the partially pyramidalised C-2, and (iii) the preference for the nucleofuge to leave anti-periplanar to the developing lone-pair at C-2.[7a] Thus, the transition

state structures shown in **Fig. 1.3b** for the S_N2' reactions of the acyclic and cyclohexenyl systems have been proposed (Houk and Coworkers, 1983).

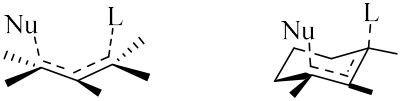
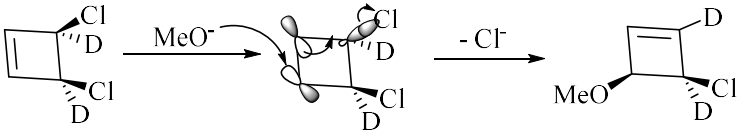


Fig. 1.3b

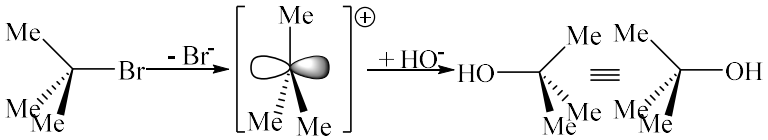
The stereochemical observation of the 4-membered substrate (**Scheme 1.14**) also supports this reasoning.



Scheme 1.14

1.3 S_N1 Mechanism

This is a two-step mechanism. The first step involves a reversible slow rate-limiting ionisation of the substrate to form a carbocation intermediate (**Scheme 1.15**). The α–centre changes its sp^3 state of hybridisation to sp^2 in the intermediate. The nucleophile then combines rapidly with the planar carbocation in the second step to yield the final product(s). The second step is the product development step. There are some direct and indirect evidences in support of the formation of the carbocation intermediate.



Scheme 1.15

The characteristic features of the S_N1 mechanism are reflected in the following observations:

[7a]This resembles Winstein's suggestion that the S_N2' reaction is a double-back-side nucleophilic displacement.

(i) *Kinetic studies*

(a) the rate is first order in the substrate and zeroth order in the reagent. Overall order is 1.[8] The energy profile diagram is presented in **Fig. 1.4.**

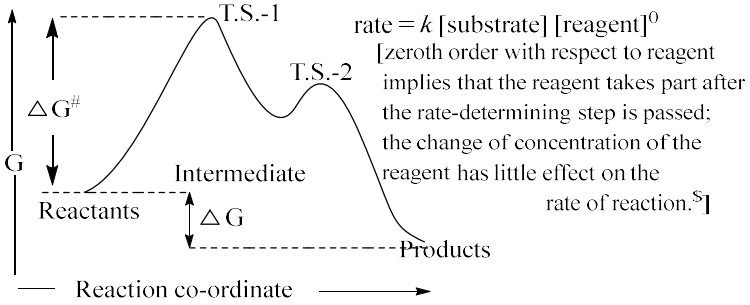


Fig. 1.4

(b) The rates of S_N1 reactions gradually increase from the methyl to primary to secondary to the tertiary substrates (see **Fig. 1.5a**). This is primarily due to the increased stability of the carbocations (methyl < primary < secondary < tertiary). By the Hammond postulate[9] the stability of the respective transition states is in the same order.

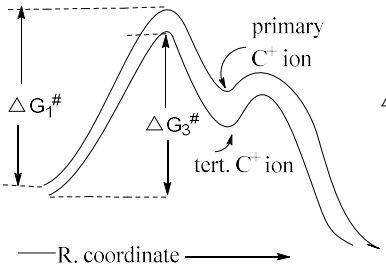
In addition, the α-branching raises the energy of the ground state more than that of the T.S. (as *the steric requirement of T.S [a tricoordinted species] is lower than that of the ground state*). The relief of the crowding assists the ionisation of the crowded substrate (**steric assistance:** see **Section 7.2** and example (d) in this section).

In going from the primary to benzyl to benzhydryl to trityl (viz. RCH_2- to $PhCH_2$- to Ph_2CH- to Ph_3C-) chlorides the stability of the carbocations increases much. Trityl chloride is thus, hydrolysed by warming in water.[10]

(c) The higher solvolytic rate of $(Me_3C)_3C$—Br (I) than Me_3C—Br (II) is probably due to the more steric assistance in the former (**Fig. 1.5b**). Both react via tertiary carbocations whose stability are supposedly quite close.

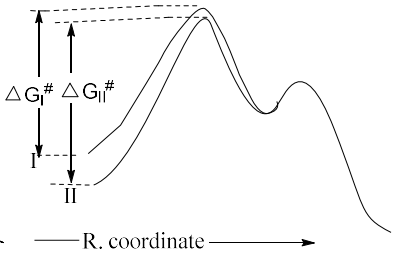
[8]If the reagent concentration is kept too low; its variation will affect the rate.

[9]According to the postulate the T.S. is closer (in the geometry, stability) to that species on either side of the curve with which its free energy difference is less; in this case the carbocation rather than the reactant in the r.d.s.



Stable C^+ ion accelerating the rate

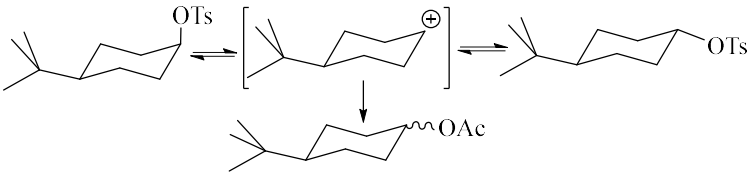
Fig. 1.5a



A case of steric assistance

Fig. 1.5b

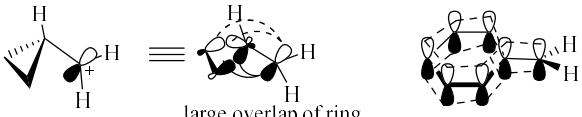
(ii) The cis-4-tert-butylcyclohexyl tosylate undergoes acetolysis at a faster rate than the corresponding trans-isomer. This is a case of steric assistance. Both the isomers go to the product(s) via a common carbocation intermediate (**Scheme 1.16**). The cis-isomer having syn-axial H/OTs interactions gets a relief of this strain upon ionisation. The trans-isomer having the equatorial –OTs does not get such assistance (**Fig. 1.5b**).



Scheme 1.16

(iii) Like S_N2, this mechanism also demands planarity around the reaction centre though in the intermediate (rather than in the T.S.). Thus, the reactions at the bridgehead of the bicyclo-compounds, A, B and C, are very slow under the unimolecular reaction conditions, too.[10a]

[10]Cyclopropylmethyl chloride also undergoes the nucleophilic substitution at a much faster rate under the solvolytic condition (S_N1). The cyclopropyl methyl cation is actually more stable than the benzyl cation.



Bisected conformation of cyclopropylmethyl cation

large overlap of ring σ–orbitals with vacant p-orbital of exocyclic C.

Benzyl cation (π-overlap)