The Walden Inversion in Nucleophilic Aliphatic Substitution Reactions

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INTRODUCTION

UNTIL 1895, when Walden (*1*) showed that inversion of the configuration of an asymmetric carbon atom can occur during substitution, it had generally been assumed that the entering group in an aliphatic substitution reaction took the place of the group displaced. The Walden Inversion was then regarded as anomalous (*2*), although some (*3, 4, 5, 6*), from the frequency of its occurrence, believed that inversion represented the normal course in substitutions.

It is the purpose of the present paper to summarize briefly the modern viewpoint on the stereochemical course of nucleophilic aliphatic substitution reactions.

MECHANISM OF NUCLEOPHILIC ALIPHATIC SUBSTITUTION REACTIONS

The discovery of the Walden Inversion had not demonstrated conclusively that inversion of configuration was the result, rather than the concomitant, of substitution. The causal relationship between substitution and inversion was first explicitly proved in 1934 by Olson and Long (*7*). In a study of the simultaneous and consecutive reactions which occur when *l*-bromosuccinic acid and chloride ion interact, they showed that inversion of configuration takes place when and only when one halogen is substituted by the other. Even more direct proof of the existence of a causal relationship came from the discovery of the fact that the velocity of substitution of a halogen on an asymmetric carbon atom by its radioactive isotope equals the velocity of racemization of the compound (*8, 9, 10*).

Since the Walden Inversion occurs only when one group on an asymmetric carbon atom is substituted by another, the mechanism by which substitution occurs has been considered to be of primary importance in the determination of the stereochemical course of a reaction.

The numerous theories which have been advanced of the mechanism of substitution are fundamentally of two types. Most of the earlier theories postulated that substitution is preceded by addition of the reagent to the compound (*5, 11, 12, 13*). Similar to this is the idea of simultaneous addition and dissociation (*14*). The second viewpoint postulated an ionization of the compound to be substituted, followed by reaction of the ion with the reagent (*15, 16, 17*).

Since 1933 Ingold and Hughes have developed a comprehensive theory of nucleophilic substitution which correlates much of the earlier theoretical and experimental work and which is substantiated by their own extensive experimental studies (*18, 19, 20, 21, 22, 23*).

Briefly, the Ingold-Hughes theory assumes that nucleophilic substitution reactions may take place by *either* of the previously postulated mechanisms:

(1) An intermediate transition complex may be formed, or, in the limit, the entry of the substituting agent into the molecule may occur simultaneously with the ejection of the group substituted. This process can be formulated, using the hydrolysis of the compound, RX, as an example:

$$RX + OH^- \rightarrow ROH + X^-$$
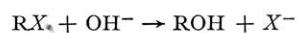
(2) The reacting molecule may ionize slowly[1] and the carbonium ion then undergoes rapid reaction with the reagent:

$$RX \underset{\longleftarrow}{\overset{slow}{\longrightarrow}} R^+ + X^-$$

$$R^+ + OH^- \xrightarrow{rapid} ROH$$
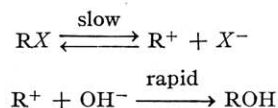
For reactions in which the solvent is not involved and the concentrations of both reactants are therefore small, the first mechanism should lead to second-order kinetics, and the second to first-order[2]; many examples of both types have been observed experimentally (*26, 30, 31, 32, 33, 34, 35*).

For reactions in which the solvent takes part, both mechanisms would show, in first approximation, first-order kinetics; but methods which involve a more detailed examination of the structural, reagent, solvent, and salt effects have been advanced to distinguish between the two paths (*18, 36*).

In general, it can be said that the compound to be substituted, the substituting agent, and the solvent determine which mechanism will prevail (*20, 34*). The unimolecular path in nucleophilic substitutions is, in general, favored when the tendency for R to lose electrons and for X to gain them is great, when the reagent has low nucleophilic activity or is present in low concentrations, or when the solvent has high ionizing capacity; the bimolecular path is favored by the reverse

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[1] Objections to an ionization mechanism have been raised on the grounds that activation energies required for the ionization would be very large (*24, 25*). Hughes and Ingold (*26*) and Bartlett (*27*) have, however, pointed out that the energy of solvation of the ions would be sufficient for the unimolecular process.
This process has also been termed "multimolecular" by Hammett (*28, 29*) in order to emphasize the role of the solvent in the ionization.

[2] First-order kinetics are to be expected for the unimolecular substitution only in the limit, as two other effects, a mass-law effect and an ionic-strength effect, cause in general more or less marked deviations. These have been predicted theoretically and observed experimentally (*20, 30*).
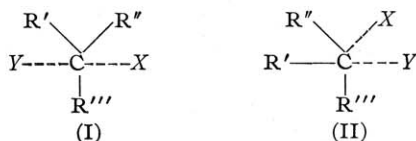
conditions. The type of mechanism involved in a reaction can be determined by a systematic study of each of these factors. In some cases, as in the hydrolysis of isopropyl bromide in aqueous ethyl alcohol, it is found that both paths are followed simultaneously (*37, 38*).

THE WALDEN INVERSION

From studies of optically active compounds, Hughes and Ingold have been able to correlate the configuration of the product in nucleophilic substitution reactions with the mechanism of reaction (*18, 19, 22, 39*).

Bimolecular substitution reactions were found to lead invariably to inversion of configuration[3]; unimolecular substitution resulted in retention of configuration, inversion, or racemization (*18, 39*).

Inversion of configuration is believed to be the normal course for bimolecular substitution reactions because the energy of the transition state leading to inversion (I) will be smaller than that corresponding to retention of configuration (II).

$$
\begin{array}{ccc}
R'\diagdown \quad \diagup R'' & \qquad & R''\diagdown \quad \diagup X \\
Y\text{----}C\text{----}X & & R'\text{----}C\text{----}Y \\
\vert & & \vert \\
R''' & & R''' \\
\text{(I)} & & \text{(II)}
\end{array}
$$

Dipolar forces which would tend to favor the attack of an ionic reagent on one side of the molecule are believed to be of little importance.

The configuration of the product in a unimolecular substitution reaction is believed to depend on the carbonium ion formed. In the absence of any group which tends to influence the configuration of the carbonium ion, it is postulated that a short-lived ion will be partially protected from the attack of the reagent on the side of the retreating anion; hence inversion of configuration with some racemization will result. If the carbonium ion is longer-lived, either because of an intrinsically small reactivity or because of the great dilution of the reagent, it will tend to have a planar structure (*27*) and will give a racemic product.

If the carbonium ion has a charged negative group which tends to stabilize the ion and to preserve the

pyramidal configuration, retention of configuration, either partial or complete, will result.

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[3] Several other workers have also advanced, chiefly on theoretical grounds, the idea that bimolecular substitution leads to inversion (*40, 41, 42*).

"Man has consumed more metal so far in the 20th century than in all previous history. With only about 5 per cent of the world's population, we in the United States have used nearly 50 per cent of the metals in the past generation. Has the United States reached its peak of metal consumption? I prefer to believe that it has not."— Dr. Jeffries