4

Nucleophilic Substitution

Introduction

Nucleophilic substitution at tetravalent (sp^3) carbon is a fundamental reaction of broad synthetic utility and has been the subject of detailed mechanistic study. An interpretation that laid the basis for current understanding was developed in England by C. K. Ingold and E. D. Hughes in the 1930s.[1] Organic chemists have continued to study substitution reactions; much detailed information about these reactions is available and a broad mechanistic interpretation of nucleophilic substitution has been developed from the accumulated data. At the same time, the area of nucleophilic substitution also illustrates the fact that while a broad conceptual framework can outline the general features to be expected for a given system, finer details reveal distinctive aspects that are characteristic of specific systems. As the chapter unfolds, the reader will come to appreciate both the breadth of the general concepts and the special characteristics of some of the individual systems.

4.1. Mechanisms for Nucleophilic Substitution

Nucleophilic substitution reactions may involve several different combinations of charged and uncharged species as reactants. The equations in Scheme 4.1 illustrate the four most common charge types. The most common reactants are neutral halides or sulfonates, as illustrated in Parts A and B of the scheme. These compounds can react with either neutral or anionic nucleophiles. When the nucleophile is the solvent, as in Entries 2 and 3, the reaction is called a *solvolysis*. Reactions with anionic nucleophiles, as in Entries 4 to 6, are used to introduce a variety of substituents such as cyanide and azide. Entries 7 and 10 show reactions that involve sulfonium ions, in which a neutral sulfide is the leaving group. Entry 8 involves generation of the diphenylmethyl diazonium ion by protonation of diphenyldiazomethane. In this reaction, the leaving

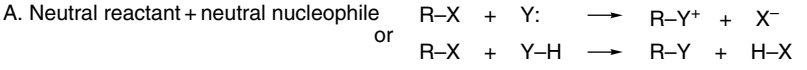
[1] C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, 2nd Edition, Cornell University Press, Ithaca, NY, 1969.

group is molecular nitrogen. Alkyl diazonium ions can also be generated by nitrosation of primary amines (see Section 4.1.5). Entry 9 is a reaction of an oxonium ion. These ions are much more reactive than sulfonium ions and are usually generated by some in situ process.

The reactions illustrated in Scheme 4.1 show the relationship of reactants and products in nucleophilic substitution reactions, but say nothing about mechanism. In

Scheme 4.1. Representative Nucleophilic Substitution Reactions

A. Neutral reactant + neutral nucleophile



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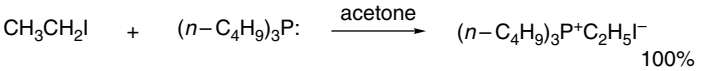
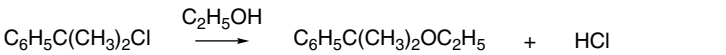
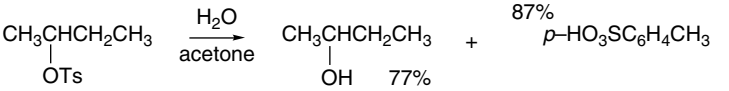


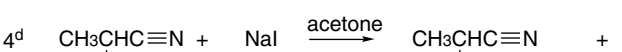
2[b]



3[c]



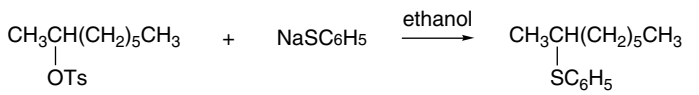
B. Neutral reactant + anionic nucleophile



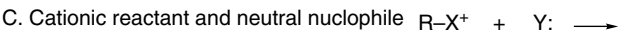
4[d]

5[e]

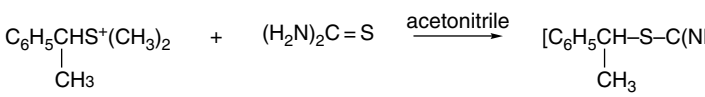
6[f]



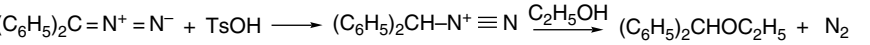
C. Cationic reactant and neutral nuclophile



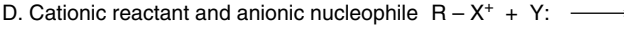
7[g]



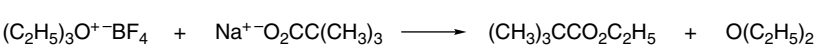
8[h]



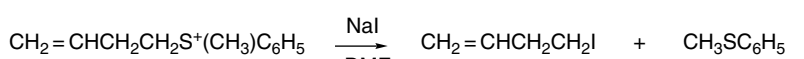
D. Cationic reactant and anionic nucleophile



9[j]



10[j]



a. S. A. Buckler and W. A. Henderson, *J. Am. Chem. Soc.*, **82**, 5795 (1960).
b. R. L. Buckson and S. G. Smith, *J. Org. Chem.*, **32**, 634 (1967).
c. J. D. Roberts, W. Bennett, R. E. McMahon, and E. W. Holroyd, *J. Am. Chem. Soc.*, **74**, 4283 (1952).
d. M. S. Newman and R. D. Closson, *J. Am. Chem. Soc.*, **66**, 1553 (1944).
e. K. B. Wiberg and B. R. Lowry, *J. Am. Chem. Soc.*, **85**, 3188 (1963).
f. H. L. Goering, D. L. Towns, and B. Dittmar, *J. Org. Chem.*, **27**, 736 (1962).
g. H. M. R. Hoffmann and E. D. Hughes, *J. Chem. Soc.*, 1259 (1964).
h. J. D. Roberts and W. Watanabe, *J. Am. Chem. Soc.*, **72**, 4869 (1950).
i. D. J. Raber and P. Gariano, *Tetrahedron Lett.*, 4741 (1971).
j. E. J. Corey and M. Jautelat, *Tetrahedron Lett.*, 5787 (1968).

order to develop an understanding of the mechanisms of such reactions, we begin by reviewing the limiting cases as defined by Hughes and Ingold, namely the *ionization mechanism* (S_N1, substitution-nucleophilic-unimolecular) and the *direct displacement mechanism* (S_N2, substitution-nucleophilic-bimolecular). We will find that in addition to these limiting cases, there are related mechanisms that have aspects of both ionization and direct displacement.

4.1.1. Substitution by the Ionization (S_N1) Mechanism

The ionization mechanism for nucleophilic substitution proceeds by rate-determining heterolytic dissociation of the reactant to a tricoordinate *carbocation*[2] and the *leaving group*. This dissociation is followed by rapid combination of the electrophilic carbocation with a Lewis base (*nucleophile*) present in the medium. A potential energy diagram representing this process for a neutral reactant and anionic nucleophile is shown in Figure 4.1.

The ionization mechanism has several distinguishing features. The ionization step is rate determining and the reaction exhibits first-order kinetics, with the rate of decomposition of the reactant being *independent of the concentration and identity of the nucleophile*. The symbol assigned to this mechanism is S_N1, for *substitution*, *nucleophilic*, *unimolecular*:

$$\text{R–X} \xrightarrow[\text{slow}]{k_1} \text{R}^+ + \text{X}^-$$

$$\text{R}^+ + \text{Y}^- \xrightarrow[\text{fast}]{k_2} \text{R–Y}$$

$$\text{rate} = k_1[\text{R–X}]$$

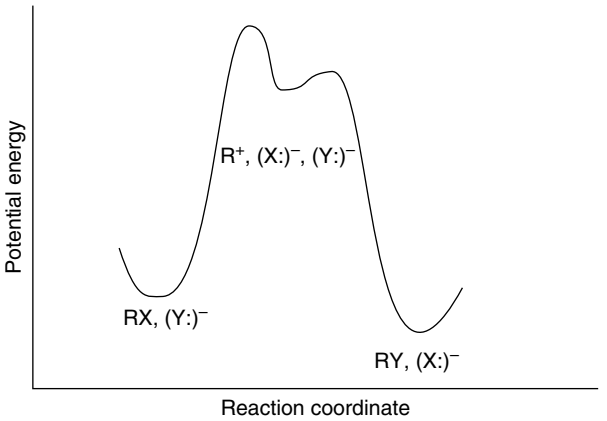


Fig. 4.1. Reaction energy profile for nucleophilic substitution by the ionization (S_N1) mechanism.

[2] Tricoordinate carbocations were originally called *carbonium ions*. The terms methyl cation, butyl cation, etc., are used to describe the corresponding tricoordinate cations. *Chemical Abstracts* uses as specific names methylium, ethylium, 1-methylethylium, and 1,1-dimethylethylium to describe the methyl, ethyl, 2-propyl, and *t*-butyl cations, respectively. We use *carbocation* as a generic term for carbon cations. The term *carbonium ion* is now used for pentavalent positively charged carbon species.

As the rate-determining step is endothermic with a late TS, application of *Hammond's postulate* (Section 3.3.2.2) indicates that the TS should resemble the product of the first step, the carbocation intermediate. Ionization is facilitated by factors that lower the energy of the carbocation or raise the energy of the reactant. The rate of ionization depends primarily on reactant structure, including the identity of the leaving group, and the solvent's ionizing power. The most important electronic effects are stabilization of the carbocation by electron release, the ability of the leaving group to accept the electron pair from the covalent bond that is broken, and the capacity of the solvent to stabilize the charge separation that develops in the TS. Steric effects are also significant because of the change in coordination that occurs on ionization. The substituents are spread apart as ionization proceeds, so steric compression in the reactant favors ionization. On the other hand, geometrical constraints that preclude planarity of the carbocation are unfavorable and increase the energy required for ionization.

The ionization process is very sensitive to solvent effects, which are dependent on the charge type of the reactants. These relationships follow the general pattern for solvent effects discussed in Section 3.8.1. Ionization of a neutral substrate results in charge separation, and solvent polarity has a greater effect at the TS than for the reactants. Polar solvents lower the energy of the TS more than solvents of lower polarity. In contrast, ionization of cationic substrates, such as trialkylsulfonium ions, leads to dispersal of charge in the TS and reaction rates are moderately retarded by more polar solvents because the reactants are more strongly solvated than the TS. These relationships are illustrated in Figure 4.2.

Stereochemical information can add detail to the mechanistic picture of the S_N1 substitution reaction. The ionization step results in formation of a carbocation intermediate that is planar because of its sp^2 hybridization. If the carbocation is sufficiently long-lived under the reaction conditions to diffuse away from the leaving group, it becomes symmetrically solvated and gives racemic product. If this condition is not met, the solvation is dissymmetric and product can be obtained with net retention or inversion of configuration, even though an achiral carbocation is formed. The extent of inversion or retention depends on the specific reaction. It is frequently observed that there is net *inversion of configuration*. The stereochemistry can be interpreted in terms of three different stages of the ionization process. The contact ion pair represents

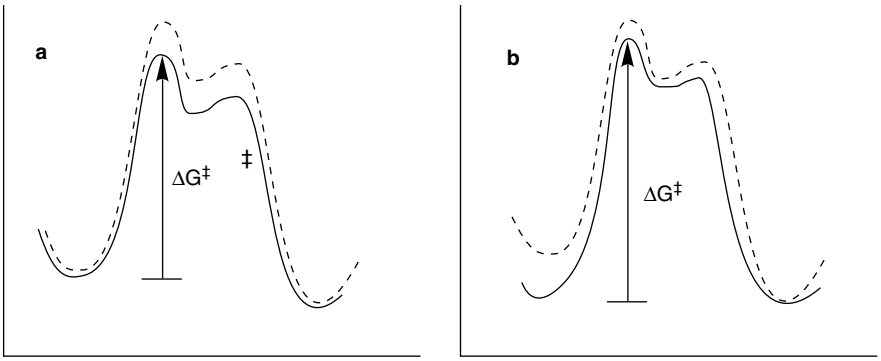
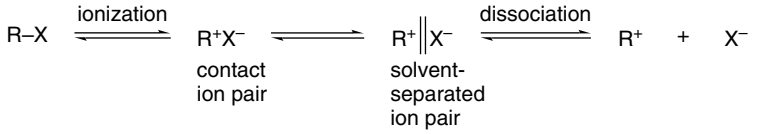


Fig. 4.2. Solid line: polar solvent; dashed line: nonpolar solvent. (a) Solvent effects on R–X $\rightarrow$ $R^+ + X^-$. Polar solvents increase the rate by stabilization of the $R^{\delta+}\text{---}X^{\delta-}$ transition state. (b) Solvent effect on R–$X^+ \rightarrow R^+ + X$. Polar solvents decrease the rate because stabilization of R-$\text{-}^{\delta+}\text{-}$X transition state is less than for the more polar reactant.

a very close association between the cation and anion formed in the ionization step. The solvent-separated ion pair retains an association between the two ions, but with intervening solvent molecules. Only at the dissociation stage are the ions independent and the carbocation symmetrically solvated. The tendency toward net inversion is believed to be due to electrostatic shielding of one face of the carbocation by the anion in the ion pair. The importance of ion pairs is discussed further in Sections 4.1.3 and 4.1.4.



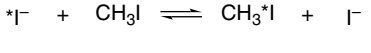
According to the ionization mechanism, if the same carbocation can be generated from more than one precursor, its subsequent reactions should be independent of its origin. But, as in the case of stereochemistry, this expectation must be tempered by the fact that ionization initially produces an ion pair. If the subsequent reaction takes place from this ion pair, rather than from the completely dissociated and symmetrically solvated ion, the leaving group can influence the outcome of the reaction.

4.1.2. Substitution by the Direct Displacement (S_N2) Mechanism

The direct displacement mechanism is concerted and proceeds through a single rate-determining TS. According to this mechanism, the reactant is attacked by a nucleophile from the side opposite the leaving group, with bond making occurring simultaneously with bond breaking between the carbon atom and the leaving group. The TS has trigonal bipyramidal geometry with a pentacoordinate carbon. These reactions exhibit second-order kinetics with terms for both the reactant and nucleophile:

$$\text{rate} = k[\text{R-X}][\text{Nu :}]$$

The mechanistic designation is S_N2 for *substitution*, *nucleophilic*, *bimolecular*. A reaction energy diagram for direct displacement is given in Figure 4.3. A symmetric diagram such as the one in the figure would correspond, for example, to exchange of iodide by an S_N2 mechanism.



The frontier molecular orbital approach provides a description of the bonding interactions that occur in the S_N2 process. The frontier orbitals are a filled nonbonding orbital on the nucleophile **Y**: and the σ^* antibonding orbital associated with the carbon undergoing substitution and the leaving group **X**. This antibonding orbital has a large lobe on carbon directed away from the C−X bond.[3] Back-side approach by the nucleophile is favored because the strongest initial interaction is between the filled orbital on the nucleophile and the antibonding σ^* orbital. As the transition state is approached, the orbital at the substitution site has *p* character. The MO picture predicts that the reaction will proceed with inversion of configuration, because the development

[3] L. Salem, *Chem. Brit.*, **5**, 449 (1969); L. Salem, *Electrons in Chemical Reactions: First Principles*, Wiley, New York, 1982, pp. 164–165.

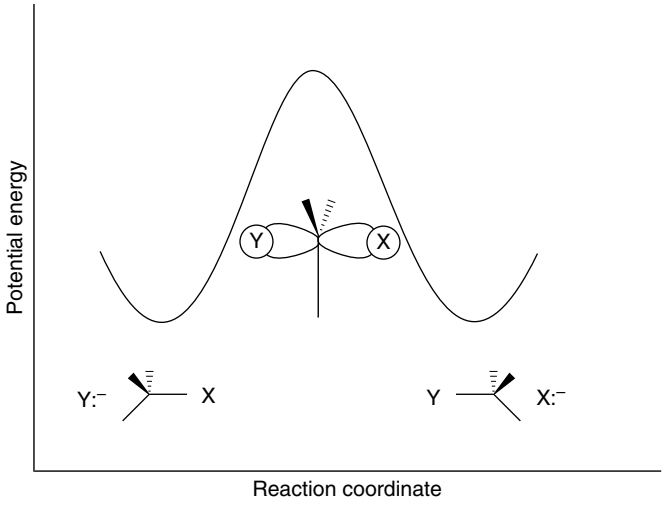
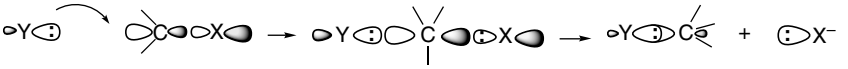
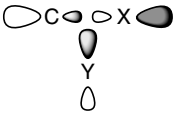


Fig. 4.3. Reaction energy profile for nucleophilic substitution by the direct displacement (S_N2) mechanism.

of the TS is accompanied by rehybridization of the carbon to the trigonal bipyramidal geometry. As the reaction proceeds on to product, sp^3 hybridization is reestablished in the product with inversion of configuration.



Front-side approach is disfavored because the density of the σ* orbital is less in the region between the carbon and the leaving group and, as there is a nodal surface between the atoms, a front-side approach would involve both a bonding and an antibonding interaction with the σ* orbital.



The direct displacement (S_N2) mechanism has both kinetic and stereochemical consequences. S_N2 reactions exhibit second-order kinetics—first order in both reactant and nucleophile. Because the nucleophile is intimately involved in the rate-determining step, not only does the rate depend on its concentration, but the nature of the nucleophile is very important in determining the rate of the reaction. This is in sharp contrast to the ionization mechanism, in which the identity and concentration of the nucleophile do not affect the rate of the reaction.

$$\text{R–X} + \text{Y:}^- \xrightarrow{k} \text{R–Y} + \text{X:}^-$$

$$\text{rate} = -\frac{d[\text{R–X}]}{dt} = -\frac{d[\text{Y:}^-]}{dt} = k[\text{R–X}][\text{Y:}^-]$$

Owing to the fact that the degree of coordination increases at the reacting carbon atom, the rates of S_N2 reactions are very sensitive to the steric bulk of the substituents.

The optimum reactant from a steric point of view is CH_3–X, because it provides the minimum hindrance to approach of the nucleophile. Each replacement of hydrogen by an alkyl group decreases the rate of reaction. As in the case of the ionization mechanism, the better the leaving group is able to accommodate an electron pair, the faster the reaction. Leaving group ability is determined primarily by the C−X bond strength and secondarily by the relative stability of the anion (see Section 4.2.3). However, since the nucleophile assists in the departure of the leaving group, the leaving group effect on rate is less pronounced than in the ionization mechanism.

Two of the key observable characteristics of S_N1 and S_N2 mechanisms are kinetics and stereochemistry. These features provide important evidence for ascertaining whether a particular reaction follows an ionization (S_N1) or direct displacement (S_N2) mechanism. Both kinds of observations have limits, however. Many nucleophilic substitutions are carried out under conditions in which the nucleophile is present in large excess. When this is the case, the concentration of the nucleophile is essentially constant during the reaction and the observed kinetics become *pseudo first order*. This is true, for example, when the solvent is the nucleophile (*solvolysis*). In this case, the kinetics of the reaction provides no evidence as to whether the S_N1 or S_N2 mechanism is operating. Stereochemistry also sometimes fails to provide a clear-cut distinction between the two limiting mechanisms. Many substitutions proceed with partial inversion of configuration rather than the complete racemization or inversion implied by the limiting mechanisms. Some reactions exhibit inversion of configuration, but other features of the reaction suggest that an ionization mechanism must operate. Other systems exhibit "borderline" behavior that makes it difficult to distinguish between the ionization and direct displacement mechanism. The reactants most likely to exhibit borderline behavior are secondary alkyl and primary and secondary benzylic systems. In the next section, we examine the characteristics of these borderline systems in more detail.

4.1.3. Detailed Mechanistic Description and Borderline Mechanisms

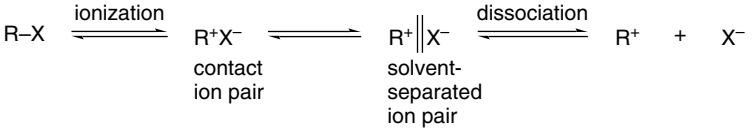
The ionization and direct displacement mechanisms can be viewed as the limits of a mechanistic continuum. At the S_N1 limit, there is *no covalent interaction* between the reactant and the nucleophile in the TS for cleavage of the bond to the leaving group. At the S_N2 limit, the bond-formation to the nucleophile is *concerted* with the bond-breaking step. In between these two limiting cases lies the borderline area in which the degree of covalent interaction with the nucleophile is intermediate between the two limiting cases. The concept of ion pairs was introduced by Saul Winstein, who proposed that there are two distinct types of ion pairs involved in substitution reactions.[4] The role of ion pairs is a crucial factor in detailed interpretation of nucleophilic substitution mechanisms.[5]

Winstein concluded that two intermediates preceding the dissociated carbocation were required to reconcile data on kinetics and stereochemistry of solvolysis reactions. The process of ionization initially generates a carbocation and counterion in immediate

[4] S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck, and G. C. Robinson, *J. Am. Chem. Soc.*, **78**, 328 (1956); S. Winstein, B. Appel, R. Baker, and A. Diaz, *Chem. Soc. Spec. Publ.*, No. 19, 109 (1965).

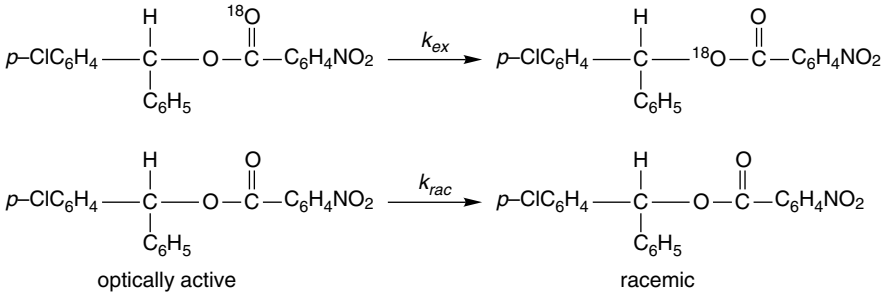
[5] J. M. Harris, *Prog. Phys. Org. Chem.*, **11**, 89 (1984); D. J. Raber, J. M. Harris, and P. v. R. Schleyer, in *Ion Pairs*, M. Szwarc, ed., John Wiley & Sons, New York, 1974, Chap. 3; T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.*, **14**, 1 (1977); J. P. Richard, *Adv. Carbocation Chem.*, **1**, 121 (1989); P. E. Dietze, *Adv. Carbocation Chem.*, **2**, 179 (1995).

proximity to one another. This species, called a contact ion pair (or intimate ion pair), can proceed to a solvent-separated ion pair in which one or more solvent molecules are inserted between the carbocation and leaving group, but in which the ions are kept together by the electrostatic attraction. The "free carbocation," characterized by symmetrical solvation, is formed by diffusion from the anion, a process known as *dissociation*.



Attack by a nucleophile or the solvent can occur at each stage. Nucleophilic attack on the contact ion pair is expected to occur with inversion of configuration, since the leaving group will shield the front side of the carbocation. At the solvent-separated ion pair stage, the nucleophile can approach from either face, particularly in the case where the solvent is the nucleophile. However, the anionic leaving group may shield the front side and favor attack by external nucleophiles from the back side. Reactions through dissociated carbocations should occur with complete *racemization*. According to this interpretation, the identity and stereochemistry of the reaction products are determined by the extent to which reaction with the nucleophile occurs on the un-ionized reactant, the contact ion pair, the solvent-separated ion pair, or the dissociated carbocation.

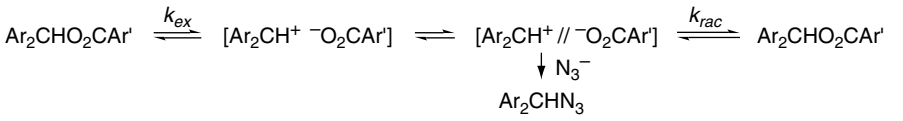
Many specific experiments support this general scheme. For example, in 80% aqueous acetone, the rate constant for racemization of *p*-chlorobenzhydryl *p*-nitrobenzoate and the rate of exchange of the ^{18}O in the carbonyl oxygen can be compared with the rate of racemization.[6] At 100 °C, $k_{ex}/k_{rac} = 2.3$.



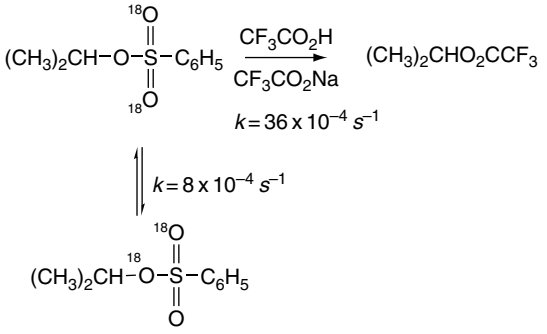
If it is assumed that ionization results in complete randomization of the ^{18}O label in the carboxylate ion, k_{ex} is a measure of the rate of ionization with ion pair return and k_{rac} is a measure of the extent of racemization associated with ionization. The fact that the rate of isotopic exchange exceeds that of racemization indicates that ion pair collapse occurs with predominant retention of configuration. This is called *internal return*. When a better nucleophile is added to the system (0.14 *M* NaN_3), k_{ex} is found to be unchanged, but no racemization of reactant is observed. Instead, the intermediate that can racemize is captured by azide ion and converted to substitution product with inversion of configuration. This must mean that the contact ion pair returns to the

[6] H. L. Goering and J. F. Levy, *J. Am. Chem. Soc.*, **86,** 120 (1964).

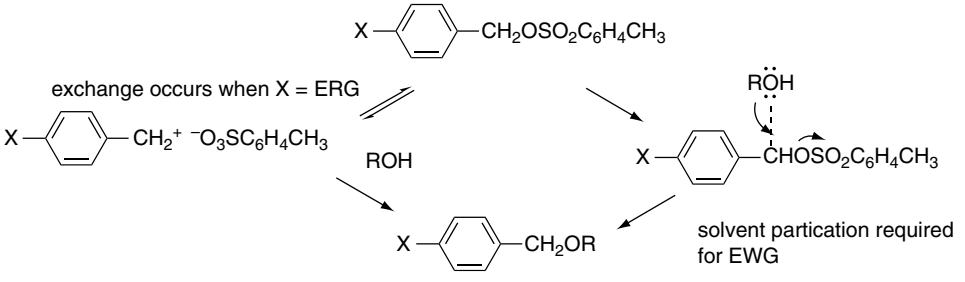
reactant more rapidly than it is captured by azide ion, whereas the solvent-separated ion pair is captured by azide ion faster than it returns to the racemic reactant.



Several other cases have been studied in which isotopic labeling reveals that the bond between the leaving group and carbon is able to break without net substitution. A particularly significant case involves secondary alkyl sulfonates, which frequently exhibit borderline behavior. During solvolysis of isopropyl benzenesulfonate in trifluoroacetic acid (TFA), it has been found that exchange among the sulfonate oxygens occurs at about one-fifth the rate of solvolysis,[7] which implies that about one-fifth of the ion pairs recombine rather than react with the nucleophile. A similar experiment in acetic acid indicated about 75% internal return.

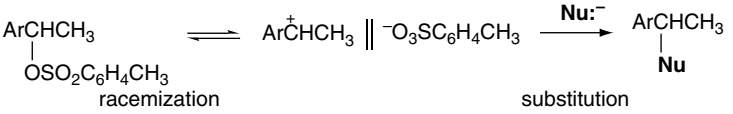


A study of the exchange reaction of benzyl tosylates during solvolysis in several solvents showed that with electron-releasing group (ERG) substituents, e.g., *p*-methylbenzyl tosylate, the degree of exchange is quite high, implying reversible formation of a primary benzyl carbocation. For an electron-withdrawing group (EWG), such as *m*-Cl, the amount of exchange was negligible, indicating that reaction occurred only by displacement involving the solvent. When an EWG is present, the carbocation is too unstable to be formed by ionization. This study also demonstrated that there was no exchange with added "external" tosylate anion, proving that isotopic exchange occurred only at the ion pair stage.[8]

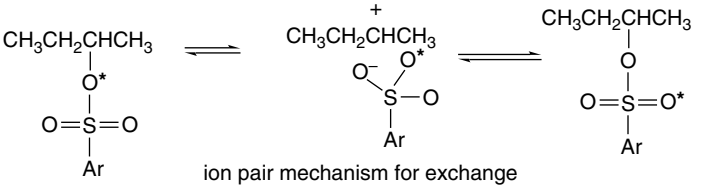


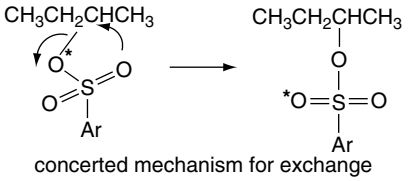
7. C. Paradisi and J. F. Bunnett, *J. Am. Chem. Soc.*, **107**, 8223 (1985).
8. Y. Tsuji, S. H. Kim, Y. Saek, K. Yatsugi, M. Fuji, and Y. Tsuno, *Tetrahedron Lett.*, **36**, 1465 (1995).

The ion pair return phenomenon can also be demonstrated by comparing the rate of racemization of reactant with the rate of product formation. For a number of systems, including l-arylethyl tosylates,[9] the rate of decrease of optical rotation is greater than the rate of product formation, which indicates the existence of an intermediate that can re-form racemic reactant. The solvent-separated ion pair is the most likely intermediate to play this role.



Racemization, however, does not always accompany isotopic scrambling. In the case of 2-butyl 4-bromobenzenesulfonate, isotopic scrambling occurs in trifluoroethanol solution without any racemization. Isotopic scrambling probably involves a contact ion pair in which the sulfonate can rotate with respect to the carbocation without migrating to its other face. The unlikely alternative is a concerted mechanism, which avoids a carbocation intermediate but requires a front-side displacement.[10]





The idea that ion pairs are key participants in nucleophilic substitution is widely accepted. The energy barriers separating the contact, solvent-separated, and dissociated ions are thought to be quite small. The reaction energy profile in Figure 4.4 depicts the three ion pair species as being roughly equivalent in energy and separated by small barriers.

The gradation from S_N1 to S_N2 mechanisms can be summarized in terms of the shape of the potential energy diagrams for the reactions, as illustrated in Figure 4.5. Curves A and C represent the S_N1 and S_N2 limiting mechanisms. The gradation from the S_N1 to the S_N2 mechanism involves greater and greater nucleophilic participation by the solvent or nucleophile at the transition state.[11] An ion pair with strong nucleophilic participation represents a mechanistic variation between the

[9] A. D. Allen, V. M. Kanagasabapathy, and T. T. Tidwell, *J. Am. Chem. Soc.*, **107**, 4513 (1985).
[10] P. E. Dietze and M. Wojciechowski, *J. Am. Chem. Soc.*, **112**, 5240 (1990).
[11] T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.*, **14**, 1 (1977).

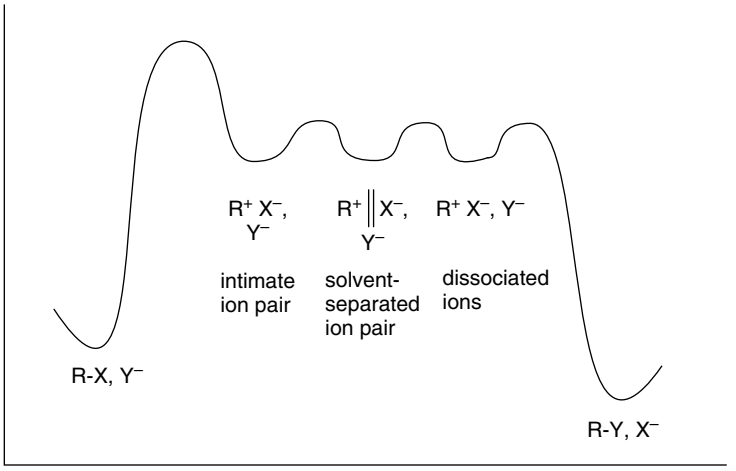
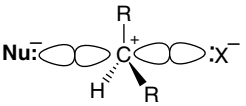


Fig. 4.4. Schematic relationship between reactants, ion pairs, and products in substitution proceeding through ion pairs.

S_N1 and S_N2 processes. This mechanism is represented by curve B and designated S_N2(intermediate). It pictures a carbocation-like TS, but one that nevertheless requires back-side nucleophilic participation and therefore exhibits second-order kinetics.



Jencks[12] emphasized that the gradation from the S_N1 to the S_N2 mechanism is related to the stability and lifetime of the carbocation intermediate, as illustrated in Figure 4.6. In the S_N1(lim) mechanism, the carbocation intermediate has a significant lifetime and is equilibrated with solvent prior to capture by a nucleophile. The reaction

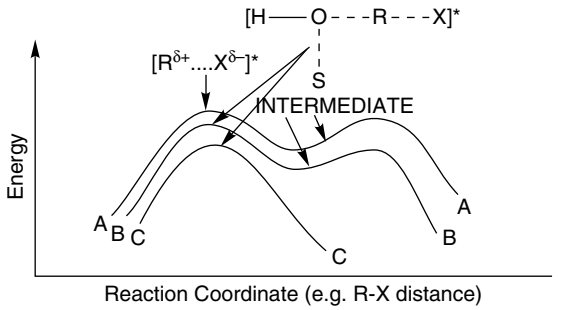


Fig. 4.5. Reaction energy profiles for substitution mechanisms. A is the S_N1 mechanism. B is the S_N2 mechanism with an intermediate ion pair or pentacoordinate species. C is the classical S_N2 mechanism. Reproduced from T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.*, **14,** 1 (1977), by permission of Academic Press.

12. W. P. Jencks, *Acc. Chem. Res.*, **13**, 161 (1980).

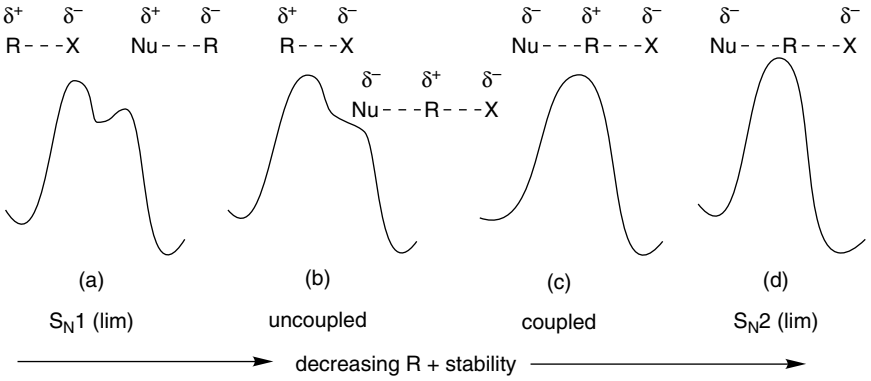
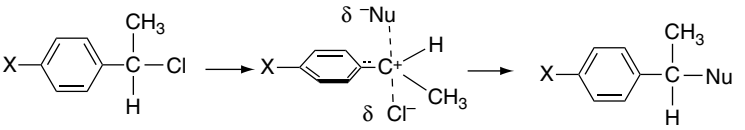


Fig. 4.6. Reaction energy profiles showing decreasing carbocation stability in change from S_N1(lim) to S_N2(lim) mechanisms.

is clearly stepwise and the energy minimum in which the carbocation intermediate resides is evident. As the stability of the carbocation decreases, its lifetime becomes shorter. The barrier to capture by a nucleophile becomes less and eventually disappears. This is described as the "uncoupled" mechanism. Ionization proceeds without nucleophilic participation but the carbocation does not exist as a free intermediate. Such reactions exhibit S_N1 kinetics, since there is no nucleophilic participation in the ionization. At still lesser carbocation stability, the lifetime of the ion pair is so short that it always returns to the reactant unless a nucleophile is present to capture it as it is formed. This type of reaction exhibits second-order kinetics, since the nucleophile must be present for reaction to occur. Jencks describes this as the "coupled" substitution process. Finally, when the stability of the (potential) carbocation is so low that it cannot form, the direct displacement mechanism [S_N2(lim)] operates. The continuum corresponds to decreasing carbocation character at the TS proceeding from S_N1(lim) to S_N2(lim) mechanisms. The degree of positive charge decreases from a full positive charge at a S_N1(lim) to the possibility of net negative charge on carbon at the S_N2(lim).

The reaction of azide ion with substituted 1-phenylethyl chlorides is an example of a coupled displacement. Although it exhibits second-order kinetics, the reaction has a substantially positive ρ value, indicative of an electron deficiency at the TS.[13] The physical description of this type of activated complex is called the "exploded" S_N2 TS.



For many secondary sulfonates, nucleophilic substitution seems to be best explained by a coupled mechanism, with a high degree of carbocation character at the TS. The bonds to both the nucleophile and the leaving group are relatively weak, and the carbon has a substantial positive charge. However, the carbocation per se has no lifetime, because bond rupture and formation occur concurrently.[14]

[13] J. P. Richard and W. P. Jencks, *J. Am. Chem. Soc.*, **106**, 1383 (1984).
[14] B. L. Knier and W. P. Jencks, *J. Am. Chem. Soc.*, **102**, 6789 (1980); M. R. Skoog and W. P. Jencks, *J. Am. Chem. Soc.*, **106**, 7597 (1984).

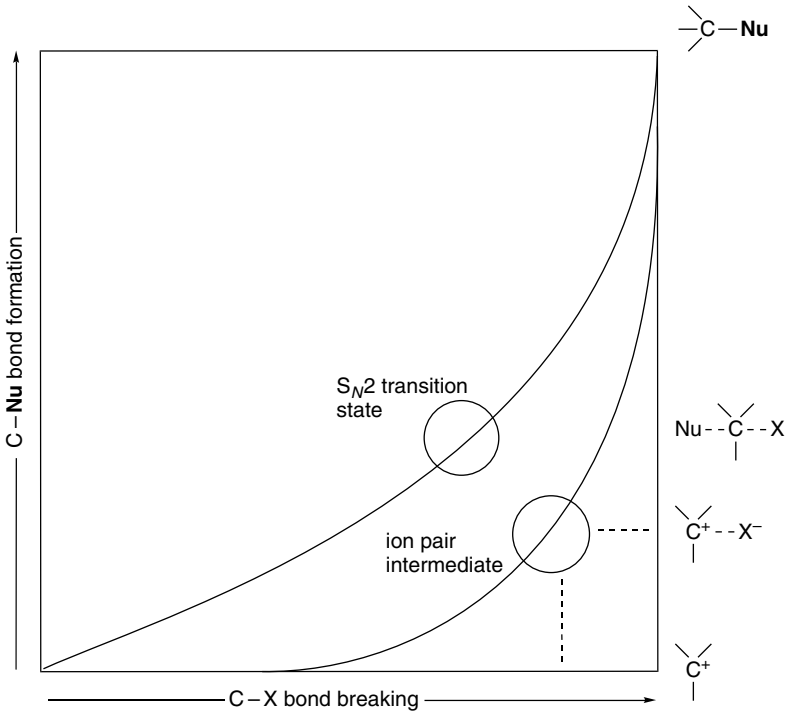


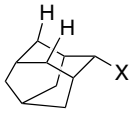
Fig. 4.7. Two-dimensional reaction energy diagram showing concerted, ion pair intermediate, and stepwise mechanisms for nucleophilic substitution.

Figure 4.7 summarizes these ideas using a two-dimensional energy diagram.[15] The S_N2(lim) mechanism corresponds to the concerted pathway through the middle of the diagram. It is favored by high-energy carbocation intermediates that require nucleophilic participation. The S_N1(lim) mechanism is the path along the edge of the diagram corresponding to separate bond-breaking and bond-forming steps. An ion pair intermediate mechanism implies a true intermediate, with the nucleophile present in the TS, but at which bond formation has not progressed. The "exploded transition state" mechanism describes a very similar structure, but one that is a transition state, not an intermediate.[16]

The importance of solvent participation in the borderline mechanisms should be noted. Solvent participation is minimized by high electronegativity and hardness, which reduce the Lewis basicity and polarizability of the solvent molecules. Trifluoroacetic acid and polyfluoro alcohols are among the least nucleophilic of the solvents commonly used in solvolysis studies.[17] These solvents are used to define the characteristics of reactions proceeding with little nucleophilic solvent participation. Solvent nucleophilicity increases with the electron-donating capacity of the molecule. The order trifluoroacetic acid (TFA) < trifluoroethanol (TFE) < acetic acid < water < ethanol gives a qualitative indication of the trend in solvent nucleophilicity. More is said about solvent nucleophilicity in Section 4.2.1.

[15] R. A. More O'Ferrall, *J. Chem. Soc. B*, 274 (1970).
[16] For discussion of the borderline mechanisms, see J. P. Richard, *Adv. Carbocation Chem.*, **1**, 121 (1989); P. E. Dietze, *Adv. Carbocation Chem.*, **2**, 179 (1995).
[17] T. W. Bentley, C. T. Bowen, D. H. Morten, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **103**, 5466 (1981).

Reactant structure also influences the degree of nucleophilic solvent participation. Solvation is minimized by steric hindrance and the 2-adamantyl system is regarded as being a secondary reactant that cannot accommodate significant back-side nucleophilic participation.



The 2-adamantyl system is used as a model reactant for defining the characteristics of ionization without solvent participation. The degree of nucleophilic participation in other reactions can then be estimated by comparison with the 2-adamantyl system.[18]

4.1.4. Relationship between Stereochemistry and Mechanism of Substitution

Studies of the stereochemistry are a powerful tool for investigation of nucleophilic substitution reactions. Direct displacement reactions by the S_N2(lim) mechanism are expected to result in complete inversion of configuration. The stereochemical outcome of the ionization mechanism is less predictable, because it depends on whether reaction occurs via an ion pair intermediate or through a completely dissociated ion. Borderline mechanisms may also show variable stereochemistry, depending upon the lifetime of the intermediates and the extent of ion pair recombination.

Scheme 4.2 presents data on some representative nucleophilic substitution processes. Entry 1 shows the use of 1-butyl-1-*d*,*p*-bromobenzenesulfonate (Bs, brosylate) to demonstrate that primary systems react with inversion, even under solvolysis conditions in formic acid. The observation of inversion indicates a concerted mechanism, even in this weakly nucleophilic solvent. The primary benzyl system in

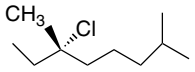
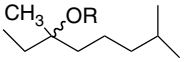
Scheme 4.2. Stereochemistry of Nucleophilic Substitution Reactions

	Reactant[a]	Conditions	Product	Sterechemistry
1[b]	$CH_3CH_2CH_2CHDOBs$	HCO_2H, 99° C	$CH_3CH_2CH_2CHDO_2CH$	99 ± 6% inv.
2[c]	$C_6H_5CHDOTs$	CH_3CO_2H, 25° C	$C_6H_5CHDO_2CCH_3$	82 ± 1% inv.
3[c]	$CH_3CH(CH_2)_5CH_3$ | OTs	$Et_4N^+{-}O_2CCH_3$, acetone, 56° C	$CH_3CH(CH_2)_5CH_3$ | O_2CCH_3	100% inv.
4[d]	$CH_3CH(CH_2)_5CH_3$ | OTs	75 % aq. dioxane, 65° C	$CH_3CH(CH_2)_5CH_3$ | OH	77% inv.
		75 % aq. dioxane, 0.06 *M* NaN_3, 65° C	$CH_3CH(CH_2)_5CH_3$ | OH 22%	100% inv.
			$CH_3CH(CH_2)_5CH_3$ | N_3 78%	100% inv.

(Continued)

[18] F. L. Schadt, T. W. Bentley, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **98**, 7667 (1976).

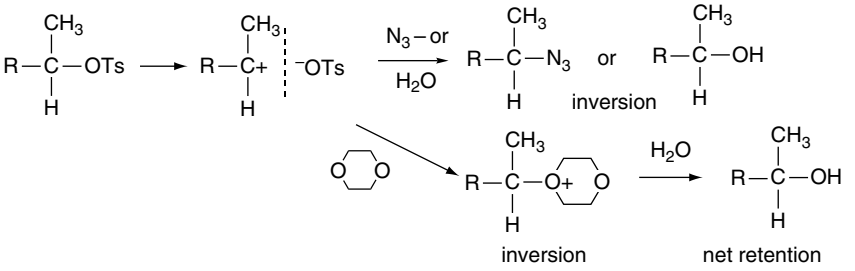
Scheme 4.2. ***(Continued)***

5[e]				
			CH_3OH, DTBP, 25° C	78% inv.
			C_2H_5OH, DTBP, 40° C	55% inv.
			HCO_2H, DTBP, 0° C	42% inv.
			CF_3CH_2OH, DTBP, 25° C	13% ret.
			t-BuOH, 20% H_2O, 25° C	49% inv.
			dioxane, 20% H_2O, 25° C	98% inv.
6[f]	$C_6H_5CHCH_3$ | Cl	$K^+{}^-O_2CCH_3$, CH_3CO_2H, 50° C	$C_6H_5CHCH_3$ | O_2CCH_3	15% inv.
		$Et_4N^+{}^-O_2CCH_3$ 50% acetone	$C_6H_5CHCH_3$ | O_2CCH_3	65% inv.
7[f]	$C_6H_5CC_2H_5$ (CH$_3$ above, OPNB below)	$K^+{}^-O_2CCH_3$, CH_3CO_2H, 23° C	$C_6H_5CC_2H_5$ (CH$_3$, $O_2CH_2CH_3$)	5 ± 2% inv.
		NaN_3 in CH_3OH, 65° C	$C_6H_5CC_2H_5$ (CH$_3$, N_3)	56 ± 1% inv.
			$C_6H_5CC_2H_5$ (CH$_3$, OCH_3)	14% inv.
		90% aq, acetone	$C_6H_5CC_2H_5$ (CH$_3$, OH)	38% ret.

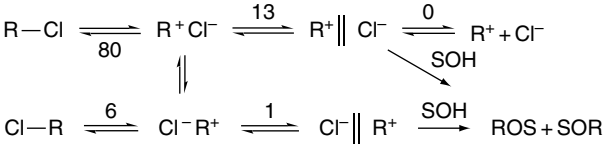
a. Abbreviations: OBs = *p*-bromobenzenesulfonate; OTs = *p*-toluenesulfonate; OPMB = *p*-nitrobenzoate; DTBP = 2,6-di-*t*-butylpyridine.
b. A. Streitwieser, Jr., *J. Am. Chem. Soc.*, **77**, 1117 (1955).
c. A. Streitwieser, Jr., T. D. Walsh, and J. R. Wolfe, *J. Am. Chem. Soc.*, **87**, 3682 (1965).
d. H. Weiner and R. A. Sneen, *J. Am. Chem. Soc.*, **87**, 287 (1965).
e. P. Muller and J. C. Rosier, *J. Chem. Soc., Perkin Trans.*, **2**, 2232 (2000).
f. J. Steigman and L. P. Hammett, *J. Am. Chem. Soc.*, **59**, 2536 (1937).
g. L. H. Sommer and F. A. Carey, *J. Org. Chem.*, **32**, 800 (1967).
h. H. L. Goering and S. Chang, *Tetrahedron Lett.* 3607 (1965).

Entry 2 exhibits high, but not complete, inversion for acetolysis, which is attributed to competing racemization of the reactant by ionization and internal return. Entry 3 shows that reaction of a secondary 2-octyl system with the moderately good nucleophile acetate ion occurs with complete inversion. The results cited in Entry 4 serve to illustrate the importance of solvation of ion pair intermediates in reactions of secondary tosylates. The data show that partial racemization occurs in aqueous dioxane but that an added nucleophile (azide ion) results in complete inversion in the products resulting from reaction with both azide ion and water. The alcohol of retained configuration is attributed to an intermediate oxonium ion resulting from reaction of the ion pair

with the dioxane solvent, which would react with water to give product of retained configuration. When azide ion is present, dioxane does not effectively compete for the ion pair intermediate and all of the alcohol arises from the inversion mechanism.[19]



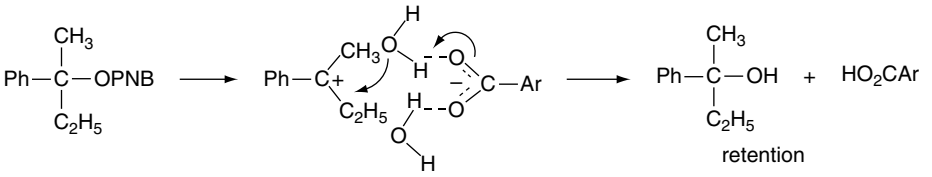
Entry 5 shows data for a tertiary chloride in several solvents. The results range from nearly complete inversion in aqueous dioxane to slight net retention in TFE. These results indicate that the tertiary carbocation formed does not achieve symmetrical solvation but, instead, the stereochemistry is controlled by the immediate solvation shell. Stabilization of a carbocation intermediate by benzylic conjugation, as in the 1-phenylethyl system shown in Entry 6, leads to substitution with extensive racemization. A thorough analysis of the data concerning stereochemical, kinetic, and isotope effects on solvolysis reactions of 1-phenylethyl chloride in several solvent systems has been carried out.[20] The system was analyzed in terms of the fate of the contact ion pair and solvent-separated ion pair intermediates. From this analysis, it was estimated that for every 100 molecules of 1-phenylethyl chloride that undergo ionization, 80 return to starting material of retained configuration, 7 return to inverted starting material, and 13 go on to the solvent-separated ion pair in 97:3 TFE-H_2O. A change to a more nucleophilic solvent mix (60% ethanol-water) increased the portion that solvolyzes to 28%.



The results in Entry 7 show that even for the tertiary benzylic substrate 2-phenyl-2-butyl *p*-nitrobenzoate, the expectation of complete racemization is not realized. In moderately nucleophilic media, such as potassium acetate in acetic acid, this ideal is almost achieved, with just a slight excess of inversion. The presence of the better nucleophile azide ion, however, leads to product with a significant (56%) degree of inversion. This result is attributed to nucleophilic attack on an ion pair prior to symmetrical solvation. More surprising is the observation of net retention of configuration in the hydrolysis of 2-phenyl-2-butyl *p*-nitrobenzoate in 90% aqueous acetone. It is possible that this is the result of preferential solvent collapse from the front side at the solvent-separated ion pair stage. The bulky tertiary system may hinder solvation from the rear side. It is also possible that hydrogen bonding between a water

19. H. Weiner and R. A. Sneen, *J. Am. Chem. Soc.*, **87**, 292 (1965).
20. V. J. Shiner, Jr., S. R. Hartshorn, and P. C. Vogel, *J. Org. Chem.*, **38**, 3604 (1973).

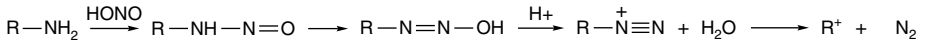
molecule and the anion of the ion pair facilitates capture of a water molecule from the front side of the ion pair.



This selection of stereochemical results points out the relative rarity of the idealized S_N1(lim) stereochemistry of complete racemization. On the other hand, the predicted inversion of the S_N2 mechanism is consistently observed, and inversion also characterizes the ion pair mechanisms with nucleophile participation. Occasionally net retention is observed. The most likely cause of retention is a double-displacement mechanism, such as proposed for Entry 4, or selective front-side solvation, as in Entry 7c.

4.1.5. Substitution Reactions of Alkyldiazonium Ions

One of the most reactive leaving groups that is easily available for study is molecular nitrogen in alkyl diazonium ions. These intermediates are generated by diazotization of primary amines. Alkyl diazonium ions rapidly decompose to a carbocation and molecular nitrogen. Nucleophilic substitution reactions that occur under diazotization conditions often differ significantly in stereochemistry, as compared with halide or sulfonate solvolysis. Recall the structural description of the alkyl diazonium ions in Section 1.4.3. The nitrogen is a very reactive leaving group and is only weakly bonded to the reacting carbon.



In contrast to an ionization process from a neutral substrate, which initially generates a contact ion pair, deamination reactions generate a cation that does not have a closely associated anion. Furthermore, since the leaving group is very reactive, nucleophilic participation is not needed for bond cleavage. The leaving group, molecular nitrogen, is quite hard, and has no electrostatic attraction to the carbocation. As a result, the carbocations generated by diazonium ion decomposition frequently exhibit rather different behavior from those generated from halides or sulfonates under solvolytic conditions.[21]

Table 4.1 shows the stereochemistry of substitution for five representative systems. Displacement at the primary 1-butyl system occurs mainly by inversion (Entry 1). However, there is also extensive formation of a rearranged product, 2-butanol (not shown in the table). Similarly, the 2-butyl diazonium ion gives 28% inversion in the unrearranged product, but the main product is *t*-butanol (Entry 2). These results indicate competition between concerted rearrangement and dissociation. Several secondary diazonium ions were observed to give alcohol with predominant

[21] C. J. Collins, *Acc. Chem. Res.*, **4**, 315 (1971); A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957); E. H. White, K. W. Field, W. H. Hendrickson, P. Dzadzic, D. F. Roswell, S. Paik, and R. W. Mullen, *J. Am. Chem. Soc.*, **114**, 8023 (1992).

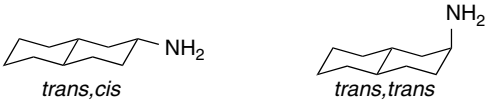
Table 4.1. Stereochemistry of Deamination in Acetic Acid

	Amine	Stereochemistry
1[a]	$CH_3CH_2CH_2CHDNH_2$	69% inv
2[b]	$CH_3CHCH_2CH_3$ (NH$_2$ on CH)	28% inv
3[c]	$PhCH_2CH_2CHCH_3$ (NH$_2$ on CH)	65% ret
4[d]	$C_6H_5-CHCH_2CH_3$ (NH$_2$ on CH)	10% ret
5[e]	$C_6H_5-C(CH_3)CH_2CH_3$ (NH$_2$ on C)	24% ret

a. D Brosch and W. Kirmse, *J. Org. Chem.*, **56**, 908 (1991).
b. K Banert, M. Bunse, T. Engberts, K.-R. Gassen, A. W. Kurminto, and W. Kirmse, *Recl. Trav. Chim. Pas-Bas*, **105**, 272 (1986).
c. N. Ileby, M. Kuzma, L. R. Heggvik, K. Sorbye, and A. Fiksdahl, *Tetrahedron: Asymmetry*, **8**, 2193 (1997).
d. R. Huisgen and C. Ruchardt, *Justus Liebigs Ann. Chem.*, **601**, 21 (1956).
e. E. H. White and J. E. Stuber, *J. Am. Chem. Soc.*, **85**, 2168 (1963).

retention when the reaction was done in acetic acid[22] (Entry 3). However, the acetate esters formed in these reactions is largely racemic. Small net retention was seen in the deamination of 1-phenylpropylamine (Entry 4). The tertiary benzylic amine, 2-phenyl-2-butylamine, reacts with 24% net retention (Entry 5). These results indicate that the composition of the product is determined by collapse of the solvent shell. Considerable solvent dependence has been observed in deamination reactions.[23] Water favors formation of a carbocation with extensive racemization, whereas less polar solvents, including acetic acid, lead to more extensive inversion as the result of solvent participation.

An analysis of the stereochemistry of deamination has also been done using 4-*t*-butylcyclohexylamines and the conformationally rigid 2-decalylamines. The results are summarized in Table 4.2.



trans,cis *trans,trans*

In solvent systems containing low concentrations of water in acetic acid, dioxane, or sulfolane, the alcohol is formed by capture of water with net retention of configuration. This result has been explained as involving a solvent-separated ion pair that

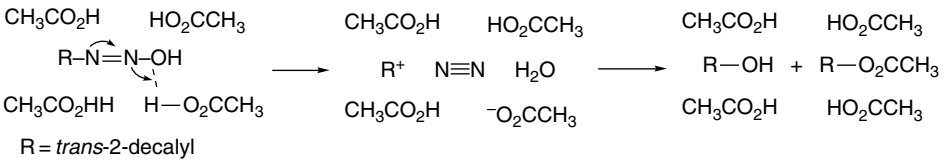
22. N. Ileby, M. Kuzma, L. R. Heggvik, K. Sorbye, and A. Fiksdahl, *Tetrahedron: Asymmetry*, **8**, 2193 (1997).
23. W. Kirmse and R. Siegfried, *J. Am. Chem. Soc.*, **105**, 950 (1983); K. Banert, M. Bunse, T. Engbert, K.-R. Gassen, A. W. Kurinanto, and W. Kirmse, *Recl. Trav. Chim. Pays-Bas*, **105**, 272 (1986).

Table 4.2. Product Stereochemistry for Deamination of Stereoisomeric Amines

	Product composition[a]			
	Alcohol		Ester	
	Retention	Inversion	Retention	Inversion
Cis-4-*t*-Butylcyclohexylamine (axial)[b]	33	8	25	33
Trans-4-*t*-Butylcyclohexylamine (equatorial)[b]	43	2	43	12
Trans,*trans*-2-Decalylamine (axial)[c]	26	2	32	40
Trans,*cis*-2-Decalylamine (equatorial)[c]	18	1	55	26

a. Composition of the total of alcohol and acetate ester. Considerable alkene is also formed.
b. H. Maskill and M. C. Whiting, *J. Chem. Soc.*, *Perkin Trans. 2*, 1462 (1976).
c. T. Cohen, A. D. Botelho, and E. Jamnkowski, *J. Org. Chem.*, **45**, 2839 (1980).

arises by concerted proton transfer and nitrogen elimination.[24] The water molecule formed in the elimination step is captured preferentially from the front side, leading to net retention of configuration for the alcohol. For the ester product, the extent of retention and inversion is more balanced, although it varies among the four systems.



It is clear from the data in Table 4.2 that the two pairs of stereoisomeric cyclic amines *do not form the same intermediate*. The collapse of the ions to product is evidently so fast that there is not time for relaxation of the initially formed intermediates to reach a common structure. Generally speaking, we can expect similar behavior for all alkyl diazonium ion decompositions. The low activation energy for dissociation and the neutral and hard character of the leaving group result in a carbocation that is free of direct interaction with the leaving group. Product composition and stereochemistry is determined by the details of the collapse of the solvent shell.

4.2. Structural and Solvation Effects on Reactivity

4.2.1. Characteristics of Nucleophilicity

The term *nucleophilicity* refers to the capacity of a Lewis base to participate in a nucleophilic substitution reaction and is contrasted with *basicity*, which is defined by the position of an equilibrium reaction with a proton donor, usually water. Nucleophilicity is used to describe trends in the rates of substitution reactions that are attributable to properties of the nucleophile. The relative nucleophilicity of a given species may be different toward various reactants and there is not an absolute scale of nucleophilicity. Nevertheless, we can gain some impression of the structural features

24. (a) H. Maskill and M. C. Whiting, *J. Chem. Soc., Perkin Trans. 2*, 1462 (1976); (b) T. Cohen, A. D. Botelhjo, and E. Jankowksi, *J. Org. Chem.*, **45**, 2839 (1970).

that govern nucleophilicity and the relationship between nucleophilicity and basicity.[25] As we will see in Section 4.4.3, there is often competition between displacement (nucleophilicity) and elimination (proton removal, basicity). We want to understand how the structure of the reactant and nucleophile (base) affect this competition.

The factors that influence nucleophilicity are best assessed in the context of the limiting S_N2 mechanism, since it is here that the properties of the nucleophile are most important. The rate of an S_N2 reaction is directly related to the effectiveness of the nucleophile in displacing the leaving group. In contrast, relative nucleophilicity has no effect on the rate of an S_N1 reaction. Several properties can influence nucleophilicity. Those considered to be most significant are: (1) the solvation energy of the nucleophile; (2) the strength of the bond being formed to carbon; (3) the electronegativity of the attacking atom; (4) the polarizability of the attacking atom; and (5) the steric bulk of the nucleophile.[26] Let us consider each how each of these factors affect nucleophilicity.

1. Strong solvation lowers the energy of an anionic nucleophile relative to the TS, in which the charge is more diffuse, and results in an increased E_a. Viewed from another perspective, the solvation shell must be disrupted to attain the TS and this desolvation contributes to the activation energy.
2. Because the S_N2 process is concerted, the strength of the partially formed new bond is reflected in the TS. A stronger bond between the nucleophilic atom and carbon results in a more stable TS and a reduced activation energy.
3. A more electronegative atom binds its electrons more tightly than a less electronegative one. The S_N2 process requires donation of electron density to an antibonding orbital of the reactant, and high electronegativity is unfavorable.
4. Polarizability describes the ease of distortion of the electron density of the nucleophile. Again, because the S_N2 process requires bond formation by an electron pair from the nucleophile, the more easily distorted the attacking atom, the better its nucleophilicity.
5. A sterically congested nucleophile is less reactive than a less hindered one because of nonbonded repulsions that develop in the TS. The trigonal bipyramidal geometry of the S_N2 transition state is sterically more demanding than the tetrahedral reactant so steric interactions increase as the TS is approached.

Empirical measures of nucleophilicity are obtained by comparing relative rates of reaction of a standard reactant with various nucleophiles. One measure of nucleophilicity is the *nucleophilic constant* (n), originally defined by Swain and Scott.[27] Taking methanolysis of methyl iodide as the standard reaction, they defined n as

$$n_{CH_3I} = \log(k_{nucl}/k_{CH_3OH}) \text{ in } CH_3OH, 25\,^\circ C$$

Table 4.3 lists the nucleophilic constants for a number of species according to this definition.

It is apparent from Table 4.3 that nucleophilicity toward methyl iodide does not correlate directly with aqueous basicity. Azide ion, phenoxide ion, and bromide are all

[25] For general reviews of nucleophilicity see R. F. Hudson, in *Chemical Reactivity and Reaction Paths*, G. Klopman, ed., John Wiley & Sons, New York, 1974, Chap. 5; J. M. Harris and S. P. McManus, eds., *Nucleophilicity*, Vol. 215, Advances in Chemistry Series, American Chemical Society, Washington, DC, 1987.

[26] A. Streitwieser, Jr., *Solvolytic Displacement Reactions*, McGraw-Hill, New York, 1962; J. F. Bunnett, *Annu. Rev. Phys. Chem.*, **14**, 271 (1963).

[27] C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, **75**, 141 (1953).

Table 4.3. Nucleophilicity Constants for Various Nucleophiles[a]

Nucleophile	n_{CH_3I}	Conjugate acid pK_a
CH_3OH	0.0	−1.7
NO_3^-	1.5	−1.3
F^-	2.7	3.45
$CH_3CO_2^-$	4.3	4.8
Cl^-	4.4	−5.7
$(CH_3)_2S$	5.3	
NH_3	5.5	9.25
N_3^-	5.8	4.74
$C_6H_5O^-$	5.8	9.89
Br^-	5.8	−7.7
CH_3O^-	6.3	15.7
HO^-	6.5	15.7
NH_2OH	6.6	5.8
NH_2NH_2	6.6	7.9
$(CH_3CH_2)_3N$	6.7	10.7
CN^-	6.7	9.3
$(CH_3CH_2)_3As$	7.1	
I^-	7.4	−10.7
HO_2^-	7.8	
$(CH_3CH_2)_3P$	8.7	8.7
$C_6H_5S^-$	9.9	6.5
$C_6H_5Se^-$	10.7	
$(C_6H_5)_3Sn^-$	11.5	

a. Data from R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, **89**, 1827 (1967); R. G. Pearson, H. Sobel, and J. Songstad, *J. Am. Chem. Soc.*, **90**, 319 (1968); P. L. Bock and G. M Whitesides, *J. Am. Chem. Soc.*, **96**, 2826 (1974).

equivalent in nucleophilicity, but differ greatly in basicity. Conversely, azide ion and acetate ion are nearly identical in basicity, but azide ion is 70 times (1.5 log units) more nucleophilic. Among neutral nucleophiles, while triethylamine is *100 times more basic* than triethylphosphine (p*Ka* of the conjugate acid is 10.7 versus 8.7), the phosphine is more nucleophilic (n is 8.7 versus 6.7), by a factor of 100 in the opposite direction. Correlation with basicity is better if the attacking atom is the same. Thus for the series of oxygen nucleophiles $CH_3O^- > C_6H_5O^- > CH_3CO_2^- > NO_3^-$, nucleophilicity parallels basicity.

Nucleophilicity usually decreases going across a row in the periodic table. For example, $H_2N^- > HO^- > F^-$ or $C_6H_5S^- > Cl^-$. This order is primarily determined by electronegativity and polarizability. Nucleophilicity increases going down the periodic table, as, e.g., $I^- > Br^- > Cl^- > F^-$ and $C_6H_5Se^- > C_6H_5S^- > C_6H_5O^-$. Three factors work together to determine this order. Electronegativity decreases going down the periodic table. Probably more important is the greater polarizability and weaker solvation of the heavier ions, which have a more diffuse electron distribution. The bond strength effect is in the opposite direction, but is overwhelmed by electronegativity and polarizability.

There is clearly a conceptual relationship between the properties called nucleophilicity and basicity. Both describe processes involving formation of a new bond to an electrophile by donation of an electron pair. The pK_a values in Table 4.3 refer to basicity toward a proton. There are many reactions in which a given chemical species might act either as a nucleophile or as a base. It is therefore of great interest to be

able to predict whether a chemical species $\mathbf{Y}:^-$ will act as a nucleophile or as a base under a given set of conditions. Scheme 4.3 lists some examples.

Basicity is a measure of the ability of a substance to attract protons and refers to an *equilibrium* with respect to a proton transfer from solvent:

$$B: + H_2O \rightleftharpoons B^+H + {}^-OH$$

These equilibrium constants provide a measure of *thermodynamic basicity*, but we also need to have some concept of *kinetic basicity*. For the reactions in Scheme 4.3, for example, it is important to be able to generalize about the rates of competing reactions. The most useful qualitative approach for making predictions is the hard-soft-acid-base (HSAB) concept[28] (see Section 1.1.6), which proposes that reactions occur most readily between species that are matched in hardness and softness. Hard nucleophiles prefer hard electrophiles, whereas soft nucleophiles prefer soft electrophiles.

The HSAB concept can be applied to the problem of competition between nucleophilic substitution and deprotonation as well as to the reaction of anions with alkyl halides. The sp^3 carbon is a soft electrophile, whereas the proton is a hard electrophile. Thus, according to HSAB theory, a soft anion will act primarily as a nucleophile, giving the substitution product, whereas a hard anion is more likely to remove a proton, giving the elimination product. Softness correlates with high polarizability and low electronegativity. The soft nucleophile–soft electrophile combination is associated with a late TS, where the strength of the newly forming bond contributes significantly to the structure and stability of the TS. Species in Table 4.3 that exhibit high nucleophilicity toward methyl iodide include CN^-, I^-, and $C_6H_5S^-$. These are soft species. Hardness

Scheme 4.3. Examples of Competition between Nucleophilicity and Basicity

S_N1 Substitution *versus*	$\mathbf{Y}:^-$ acts as a nucleophile	$\mathbf{Y}:^- + R_2C^+CHR'_2 \longrightarrow R_2CCHR'_2$ (Y)
E1 Elimination	$\mathbf{Y}:^-$ acts as a base	$\mathbf{Y}:^- + R_2C^+CHR'_2 \longrightarrow R_2C{=}CR'_2 + H{-}\mathbf{Y}$
S_N2 Substitution *versus*	$\mathbf{Y}:^-$ acts as a nucleophile	$\mathbf{Y}:^- + RCH_2CH_2X \longrightarrow RCH_2CH_2\mathbf{Y} + X^-$
E2 Elimination	$\mathbf{Y}:^-$ acts as a base	$\mathbf{Y}:^- + RCH_2CH_2X \longrightarrow RCH{=}CH_2 + H{-}\mathbf{Y}$
Nucleophilic addition to a carbonyl group	$\mathbf{Y}:^-$ acts as a nucleophile	$\mathbf{Y}:^- + RCH_2C(=O)R' \longrightarrow RCH_2C(O^-)(\mathbf{Y})R'$
Enolate formation	$\mathbf{Y}:^-$ acts as a base	$\mathbf{Y}:^- + RCH_2C(=O)R' \longrightarrow RCH{=}C(O^-)R' + H{-}\mathbf{Y}$

[28] R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, **89**, 1827 (1967); R. G. Pearson, *J. Chem. Ed.*, **45**, 581, 643 (1968); T. L. Ho, *Chem. Rev.*, **75**, 1 (1975).

Table 4.4. Hardness and Softness of Some Common Ions and Molecules

	Bases (Nucleophiles)	Acids (Electrophiles)
Soft	RSH, RS^-, I^-, R_3P $^-C{\equiv}N$, $^-{:}C{\equiv}O^+$, RCH═CHR benzene	I_2, Br_2, RS—X, RSe—X, RCH_2—X Cu(I), Ag(I), Pd(II), Pt(II), Hg(II) zero-valent metal complexes
Intermediate	Br^-, N_3^-, $ArNH_2$ pyridine	Cu(II), Zn (II), Sn,(II) R_3C^+, R_3B
Hard	NH_3, RNH_2 H_2O, HO^-, ROH, RO^-, RCO_2^-, Cl^- F^-, NO_3^-	H—X, Li^+, Na^+, R_3Si—X Mg(II), Ca(II), Al(III), Sn(IV), Ti(IV) H^+

reflects a high charge density and is associated with more electronegative elements. The hard nucleophile–hard electrophile combination implies an early TS with electrostatic attraction being more important than bond formation. For hard bases, the reaction pathway is chosen early on the reaction coordinate and primarily on the basis of charge distribution. Examples of hard bases from Table 4.3 are F^- and CH_3O^-. Table 4.4 classifies some representative chemical species with respect to softness and hardness. Numerical values of hardness were presented in Table 1.3.

Nucleophilicity is also correlated with oxidation potential for comparisons between nucleophiles involving the same element.[29] Good nucleophilicity correlates with ease of oxidation, as would be expected from the electron-donating function of the nucleophile in S_N2 reactions. HSAB considerations also suggest that nucleophilicity would be associated with species having relatively high-energy electrons. Remember that soft species have relatively high-lying HOMOs, which implies ease of oxidation.

4.2.2. Effect of Solvation on Nucleophilicity

The nucleophilicity of anions is very dependent on the degree of solvation. Many of the data that form the basis for quantitative measurement of nucleophilicity are for reactions in hydroxylic solvents. In protic hydrogen-bonding solvents, anions are subject to strong interactions with solvent. Hard nucleophiles are more strongly solvated by protic solvents than soft nucleophiles, and this difference contributes to the greater nucleophilicity of soft anions in such solvents. Nucleophilic substitution reactions of anionic nucleophiles usually occur more rapidly in polar aprotic solvents than they do in protic solvents, owing to the fact that anions are weakly solvated in such solvents (see Section 3.8). Nucleophilicity is also affected by the solvation of the cations in solution. Hard cations are strongly solvated in polar aprotic solvents such as *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide (HMPA), *N*-methylpyrrolidone (NMP), *N*,*N*-dimethylpropyleneurea

[29] M. E. Niyazymbetov and D. H. Evans, *J. Chem. Soc., Perkin Trans. 2*, 1333 (1993); M. E. Niyazymbetov, Z. Rongfeng, and D. H. Evans, *J. Chem. Soc., Perkin Trans. 2*, 1957 (1996).