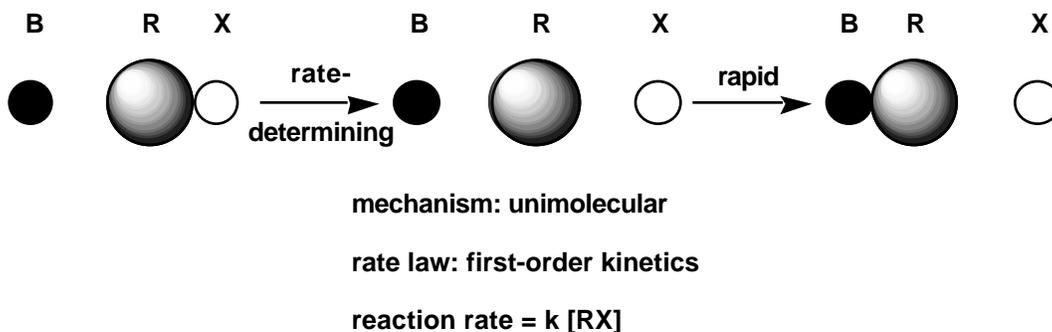
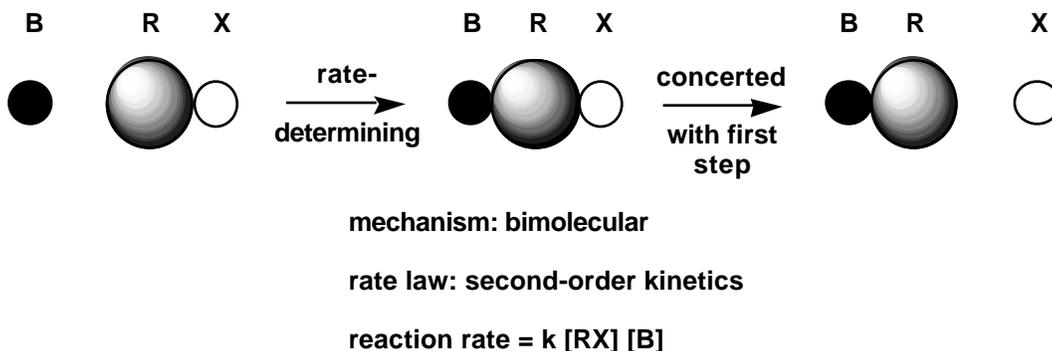


Text Related to Segment 13.02 ©2002 Claude E. Wintner

Two broad mechanistic questions which need to be examined for the substitution reactions introduced in the previous segment concern timing and stereochemical outcome. The figure illustrates the point regarding timing:

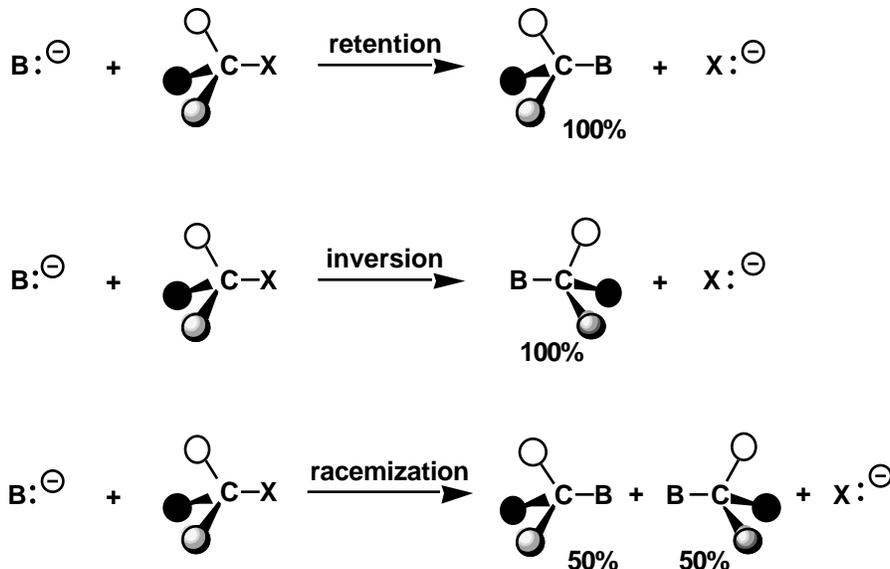


bimolecular and unimolecular reaction mechanisms

In words (first line): Does the base B attack the substrate R—X, thereby forming R—B directly and thus causing X to leave, all in a concerted manner? Or (second line) does X leave first, and does B only bind with R afterwards? If the former (a bimolecular mechanism), then the kinetics should be second-order, that is, the rate law of the reaction should depend both on the concentration of R—X and on the concentration of B. On the other hand, if the latter (a unimolecular mechanism), and if, as generally is the case, the difficult ("rate-determining") step energetically is

the breaking of the R—X bond, then the kinetics should be first-order, with the rate law depending only upon the concentration of R—X. (It is worth emphasizing the use of vocabulary in this connection: the *order* of a reaction is determined as a result of a rate law which is observed experimentally; the *mechanism* of a reaction is a working model based on a variety of evidence, including the rate law, and always subject to revision or refinement in the face of new evidence. Thus, to distinguish observed "fact" from intellectual inference, in accepted usage we speak of *first-order or second-order rate laws or kinetics*, but of *unimolecular or bimolecular mechanisms*.)

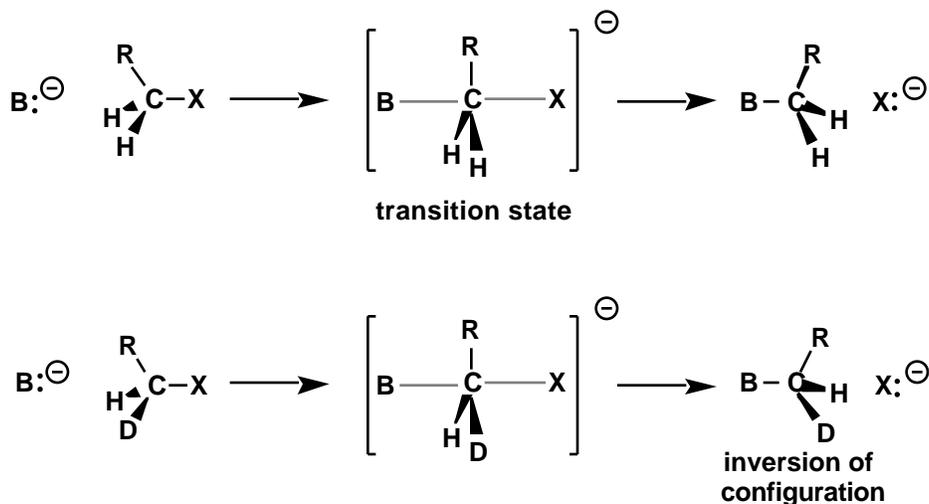
As regards stereochemical outcome, there are three limiting possibilities. The next figure illustrates how, in principle, a chiral starting material can be used to distinguish these possibilities, which will lead to three stereochemically distinct product outcomes. The reaction might be observed to proceed with *retention* of configuration at the reacting carbon center, with *inversion*, or with *racemization*:



three stereochemical outcomes for a substitution reaction

In fact, the mechanism of the reaction, and the stereochemistry of the products, are highly dependent upon the substitution pattern already existing at the

carbon atom. For the case of a *primary* halide R—CH₂—X (halide anion simply being the most commonly used leaving group in general laboratory syntheses), in which the carbon atom adjacent to the leaving halide is substituted by two hydrogen atoms and a hydrocarbon group R, second-order kinetics are observed, indicative of a bimolecular mechanism. In this circumstance the detailed reaction path is well established to be one of *rear-side* attack — relative to the leaving group — by the nucleophile, occurring at the reacting carbon center, and leading uniquely to *inversion* of configuration at that center:

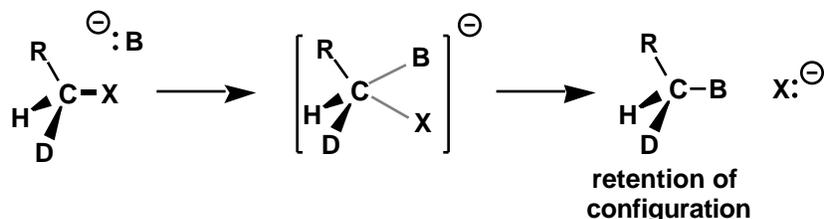


S_N2 mechanism for substitution reactions

As shown in the figure above, the attacking nucleophile approaches the reacting carbon atom coaxially with the C—X bond and from the rear, and the inversion takes place as the bonds of carbon "flip over" through the transition state, the analogy classically drawn being that of an umbrella flipping over in the wind. Of course, when the starting material is not chiral, as in the first line of the figure, the stereochemical outcome cannot be observed directly, but the inversion mechanism is safely extrapolated from other cases, most elegantly when a deuterium atom is substituted for one of the two protium atoms, as in the second line. Thus, when one

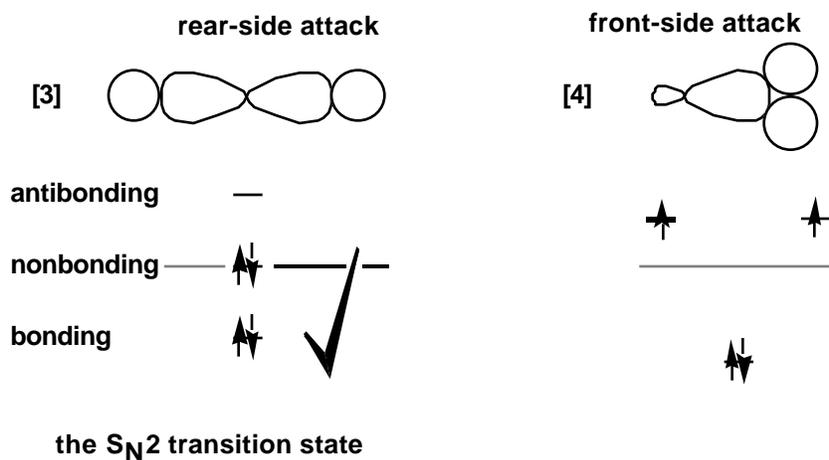
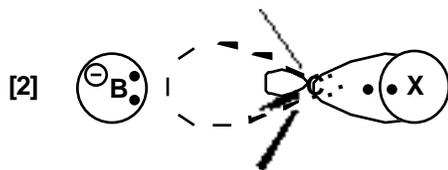
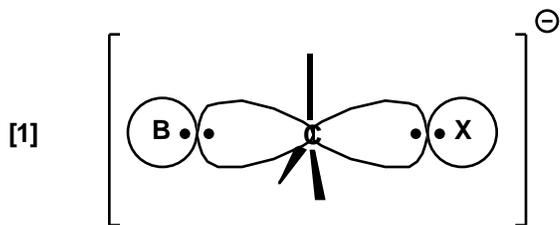
is able to begin with a single enantiomer of the substrate, one ends only with product having the antipodal configuration, as predicted by the mechanism, called the S_N2 (substitution, nucleophilic, bimolecular) mechanism.

It is important to note that a front-side mechanism would lead to *retention* of configuration:



This stereochemical result is not observed in second-order reactions involving an attacking and a leaving nucleophile at tetrahedral carbon. In fact, from polarimetric measurements it has been demonstrated that in transformations governed by the S_N2 mechanism each and every substitution event occurs with inversion; there appear not to be any "mistakes" made!

The S_N2 transition state may be viewed as an sp^2 carbon atom with the $2p_z$ orbital bonded half to the incoming group and half to the outgoing one, as shown in the following figure, line [1]. (Only orbital positions are indicated in the figure; orbital phase is not delineated.) That the attack should proceed from the rear, and coaxially, perhaps can be apprehended best by recalling that the Csp^3-X bonding orbital is fully occupied by two electrons. The electrons of the would-be donor — the attacking nucleophile B — must find an accepting orbital, and that will be the empty Csp^3-X^* antibonding orbital, which is directionally coaxial with the Csp^3-X bond, but located principally on the side opposite of the carbon atom to the leaving group X, as outlined in line [2]:



The three-molecular-orbital system of the rear-side transition state has been analyzed as having a bonding, a nonbonding, and an antibonding orbital, the entire array being filled with four electrons, so that only the bonding and nonbonding levels are occupied ([3], above); this is a pattern reminiscent of the three-orbital-four-electron systems we already have encountered. In contrast, the three-molecular-orbital system of the front-side transition state ([4], above) is regarded in a corresponding analysis as having just a single filled bonding orbital and two energetically degenerate antibonding orbitals, each occupied by a single electron (Hund's Rule). Thus, the substantial barrier to a front-side mechanism under these circumstances may be considered to be the result of this adverse orbital effect. In

fact, such an unfavorable orbital pattern also is related qualitatively to ones previously mentioned: anti-aromatic four-electron systems.

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