

**Outline**

1. Brief history and current picture of displacement reactions
2. Neighboring group participation (halogens)
3. Salt effects and ion pairs
4. Role of the solvent

**Key references**

- “Ion pairing in nucleophilic substitution reactions.” Eugene Kwan, April 2014
- “Medium effects on the rates and mechanisms of solvolytic reactions.” Bentley, T.W.; Schleyer, P.v.R. *Advances in Physical Organic Chemistry* **1977**, 14, 1-67
- “Ions and ion pairs in solvolysis reactions”. Raber, D.J.; Harris, J.M.; Schleyer, P.v.R. *Advances in Physical Organic Chemistry*. **1972**, 2, 248-274.
- “Solvolytic displacement reactions.” Streitweiser A. *Chem. Rev.* **1956**, 56, 571

Winstein S. JACS series

“The role of neighboring groups in displacement reactions.”

“Correlation of solvolysis rates.”

“Salt effects and ion pairs in solvolysis and related reactions.”

*This is a large field, this presentation will focus on mechanistic studies most relevant to dihalide solvolysis.*

**Key players**

S. Winstein  
UCLA



A. Streitweiser  
Berkeley



P. v. R. Schleyer  
(Princeton, Erlangen,  
Georgia)

**Definition of solvolysis**

First introduced by Steigman and Hammett for first-order nucleophilic displacements by solvent present in large excess. They also noted the “strange” tendency of rates: tertiary > secondary > primary.

Steigman, J. and Hammett, L. P. *JACS* **1937**, 59, 2536

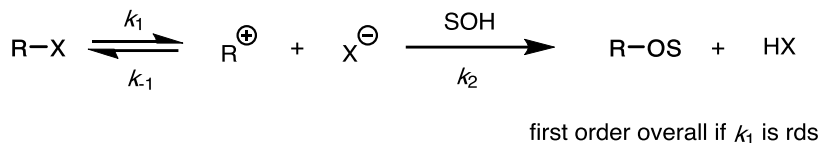
IUPAC definition. “Generally, reaction with a solvent, or with a lyonium ion or lyate ion involving the rupture of one or more bonds in the reacting solute. More specifically the term is used for substitution elimination and fragmentation reactions in which a solvent species is the nucleophile ('alcoholysis' if the solvent is an alcohol, etc.).”

**Hughes-Ingold Scheme**

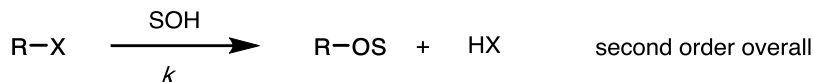
The classical mechanism details two limiting mechanisms ( $S_N1$  and  $S_N2$ ).

According to *their* theory, sometimes a combination of these two processes is operational.

Unimolecular ( $S_N1$ )

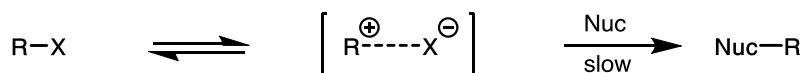
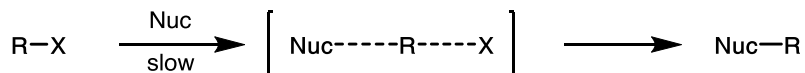
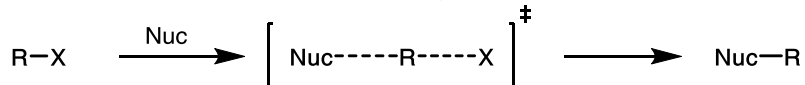


Bimolecular ( $S_N2$ )

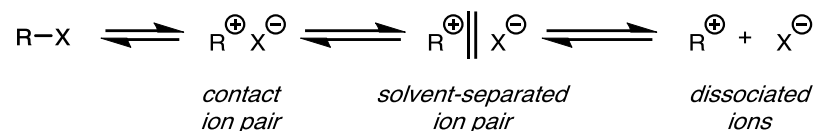


The above model does not give the full picture, especially in the case of secondary substrates.

$S_N2$ : Three possibilities: single-step, association-dissociation, contact ion-pair. These are indistinguishable by the rate law.



Winstein's modification to the  $S_N1$  mechanism involves contact ion pairs and solvent-separated ion pairs.



“It follows that, whatever detailed mechanisms might be associated with the terms  $S_N2$  and  $S_N1$ , the vital difference between  $S_N2$  and  $S_N1$  is not dependent on the extent to which the bond to the leaving group is broken but depends on whether or not nucleophilic attack occurs before the transition state in the rate-determining step.”

**Take home message**

- $S_N1$  and  $S_N2$  manifolds generally do not overlap.
- $S_N1$  reactions involve many differently dissociated ion pairs. Ionization is not always rate-determining.
- $S_N2$  reactions are often solvent-assisted.
- Secondary alkyl halides usually react through a concerted but asynchronous pathway.

Hughes and Ingold *J. Chem. Soc.* **1933**, 526  
 Bentley, T.W.; Schleyer, P.v.R. *Advances in Physical Organic Chemistry*. **1977**, *14*, 1-67  
 Winstein *JACS* **1956**, *78*, 328  
*J. Chem. Ed.* **1972**, *49*, 60; *ibid.* **2009**, *86*, 519

**Neighboring group participation**S. Winstein 20 papers in *JACS* 1942—1953.

“The role of Neighboring Groups in Replacement Reactions.”

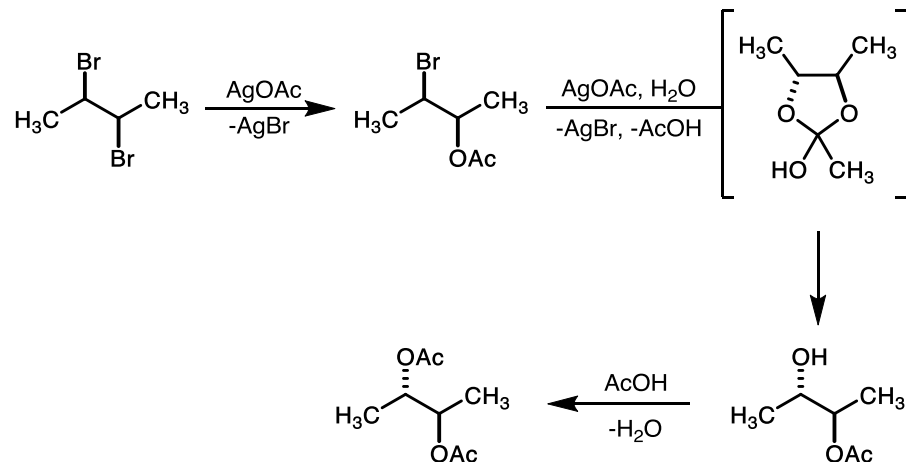
1. Retention of configuration in the reaction of some dihalides and acetoxyhalides with silver acetate. *JACS* **1942**, 2781.



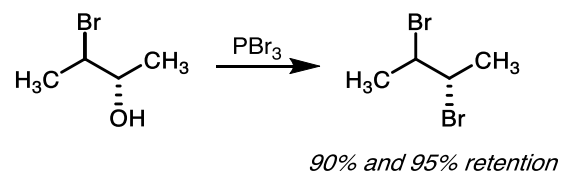
Optically active SM gives rise to inactive product due to the symmetrical nature of the cyclic intermediate.

2. The effects of small amounts of water on the reaction of silver acetate in acetic acid with some butane and cyclohexene derivatives. *JACS* **1942**, 2787.

Product is mostly inverted and some monoacetate can be isolated. Proposed mechanism:

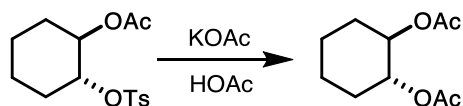


3. Retention of configuration in the reaction of the 3-bromo-2-butanols with phosphorus tribromide. *JACS* **1942**, 2791.



4. The identity of various preparations of 1,2-dibromocyclohexane. *JACS* **1942**, 2792.

5. The effect of the neighbouring acetoxy group on the course of the replacement of the tosylate group of *trans*-2-acetoxyhexyl *p*-toluenesulfonate. *JACS* **1942**, 2796.

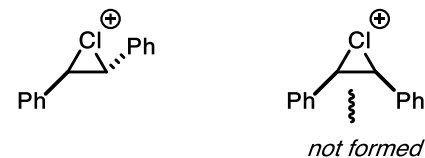
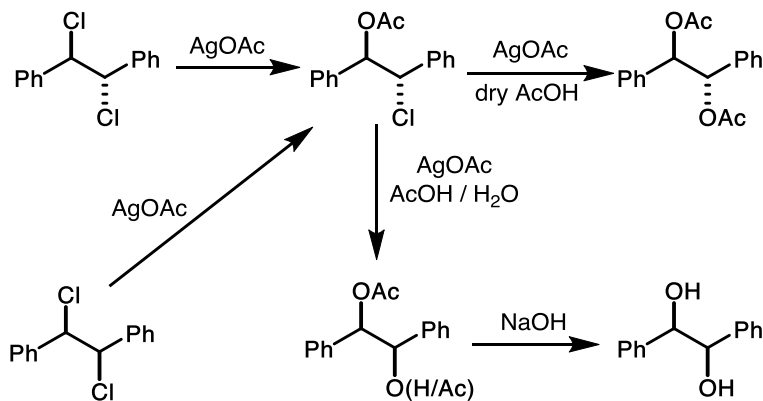


*93% retention without water*  
*100% inversion with 4% water*

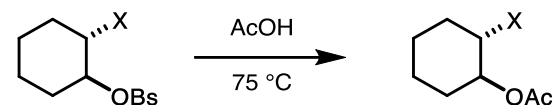
6. Cyclohexene ethyl orthoacetate. *JACS* **1943**, 613.  
Gain support for their earlier mechanistic hypotheses involving acetate as a neighboring group.

7. The methoxyl group. *JACS* **1943**, 2196.  
Show that methoxyl can also act as a neighboring group.

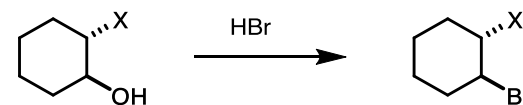
8. The reaction of stilbene dichlorides with silver acetate. *JACS* **1946**, 119.



9. "Neighboring groups and reactivity." *JACS* **1946**, 536.

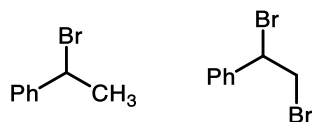


X	Rel. rate
H	1.000
OAc	0.240
Br	0.101
OMe	0.057
Cl	$4.9 \cdot 10^{-4}$
<i>cis</i> -OAc	$3.8 \cdot 10^{-4}$
<i>cis</i> -OBs	$7.7 \cdot 10^{-5}$
OBs	$6.9 \cdot 10^{-5}$
I (at rt)	1800

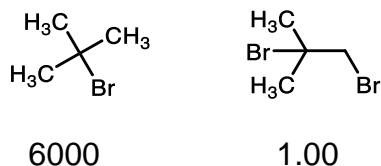


X	Rel. rate
H	1.000
I	1000
Br	0.008
Cl	$1.6 \cdot 10^{-4}$

Solvolysis in EtOH at 55 °C



Solvolysis in 80% EtOH at RT



**Conclusion:** “The neighboring group supplies a large driving force for the rate-determining ionization of the leaving group. This partly neutralizes or completely overbalances (as for I) the rate-retarding inductive effect.”

10. “Kinetics of solvolysis of *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate.” *JACS* **1948**, 812.  
First order kinetics in the presence of small amounts of water and/or acetate ion.

11. “Some reactivities involving neighboring groups.” *JACS* **1948**, 816.

Cyclohexanol and butanol derivatives investigated (all first-order kinetics)

Based on relative rates:

- *trans*-OAc, *trans*-Br and I groups form a cyclic cation
- *trans*-Cl, *cis*-OAc probably form an open carbocation

### REACTIVITY OF VARIOUS ALCOHOLS TOWARD HALOGEN ACIDS

Compound	Solvent	Half-life <i>ca.</i> 20°	Rel. rate
Cyclohexanol	Fuming HBr	20 min.	1.0
Cyclohexanol	48% HBr	7 days	1.0
Cyclohexanol	Concd. HCl	12 days	1.0
<i>trans</i> -2-Chlorocyclohexanol	Fuming HBr	85 days	$1.6 \times 10^{-4}$
<i>trans</i> -2-Bromocyclohexanol	Fuming HBr	4 hr.	0.08
<i>trans</i> -2-Iodocyclohexanol	48% HBr	<i>ca.</i> 15 min.	700
<i>trans</i> -2-Iodocyclohexanol	Concd. HCl	<i>ca.</i> 15 min.	1200
2-Butanol	Fuming HBr	75 min.	1.0
2-Butanol	48% HBr	76 hr.	...
<i>threo</i> -3-Bromo-2-butanol	Fuming HBr	3 hr.	0.4
Mixed 3-chloro-2-butanols	Fuming HBr	No halide layer in 25 days	$3 \times 10^{-40}$
<i>t</i> -Butyl alcohol	Concd. HCl	45 sec.	...

<sup>a</sup> Conservative estimate.

12. “Rates of acetolysis of 2-substituted cyclohexyl benzenesulfonates” *JACS* **1948**, 821.

- Relative rates:  
*trans*-I (1120) > *trans*-OAc (0.305) > *trans*-Br (0.0718) > *trans*-OCH<sub>3</sub> (0.0528) > *cis*-OAc ( $1.31 \times 10^{-4}$ ) > *trans*-Cl ( $0.94 \times 10^{-4}$ ) > *cis*-OBs ( $1.6 \times 10^{-5}$ ) > *trans*-OBs ( $1.4 \times 10^{-5}$ )
- Variations are largely due to *H*

13. “General theory of neighboring groups and reactivity.” *JACS* **1948**, 828.

Summary of previous papers.

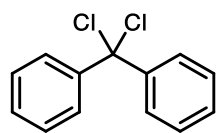
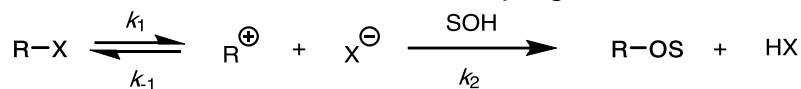
**Salt effects and ion pairs**

There can be ionic intermediates in both  $S_N1$  and  $S_N2$  reactions. Salt effects can play a role in both cases.

Common ion rate depression

The Hughes-Ingold scheme predicts that:

- Adding  $X^-$  would depress the rate of  $S_N1$ -type processes
- Rate would slow down as reaction progresses



$H_2O / acetone$

$[Cl^-]_0$ (mM)	rel. rate
0.80	4.71
5.88	3.91
26.20	2.45

Common ion exchange

If isotopically labelled  $MX$  is added, labelled  $RX$  should be possible to isolate.

- Anomalous case inconsistent with Hughes-Ingold scheme.
- Winstein suggests additional ion-pair species (contact and solvent-separated).

*JACS* **1956**, 78, 328

Normal salt effects

- Added salts increase the dielectric constant of the medium.
- This can lead to stabilization of charged intermediates.
- Overall rate acceleration is expected.

$$k = k_0 ( 1 + b [\text{salt}] )$$

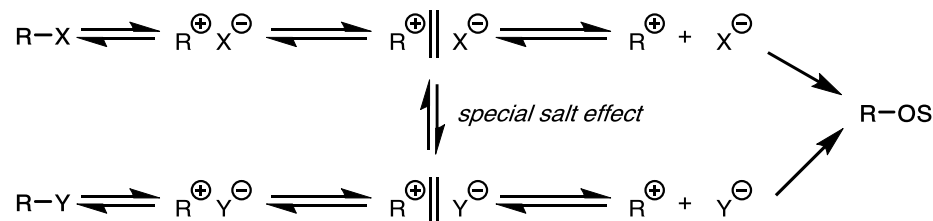
- N.B. in organic solvents inorganic salts may be contact ion pairs.
- $\sqrt{[\text{salt}]}$  can give better correlation
- Difficult to predict and strongly dependent on several factors.

Winstein *JACS* **1956**, 78, 2780

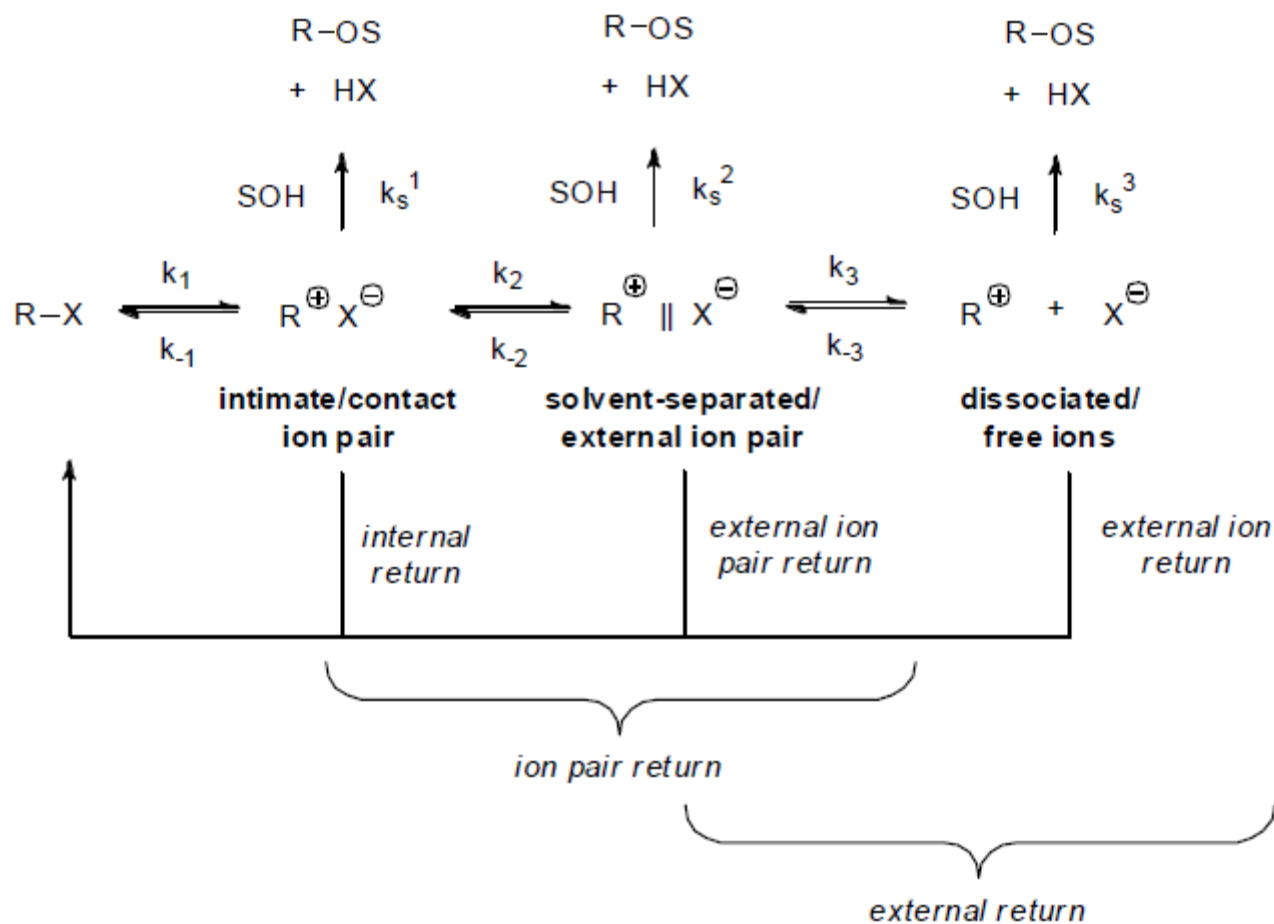
Special salt effects

- Often greater rate enhancement at low salt concentration (suppression of ion-pair return).
- At higher salt concentrations system behaves like normal salt effects.

Winstein *JACS*, **1961**, 83, 4986



“Ions and ion pairs in organic reactions.” Raber, D.J.; Harris, J.M.; Schleyer, P.v.R. *Advances in Physical Organic Chemistry*. **1972**, 2, 248-274.



- Depression only occurs if free ions are formed appreciably and carbocation is relatively stable.
- Common ion exchange can occur onSSIP and free ions.
- Special salt effect:SSIP.
- Shenvi: contact ion pair – inversion.

## Role of the solvent

### The solvent as an ionizing medium

$$\log (k / k_0)_{\text{RX}} = mY$$

$m=1$  for *t*-BuCl at rt,  $k$  is the rate constant for any solvolysis in any solvent and  $k_0$  that for solvolysis in 80% EtOH / water, which is assigned  $Y=0$ .

- Several scales exist.
- Method of measurement is not consistent between different solvents: titration, conductance, etc.
- Therefore, high ionizing power does not mean that the resulting carbocation is easily attacked by nucleophiles.

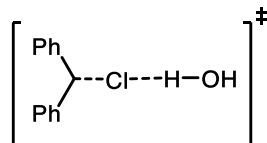
Some strongly ionizing solvents ( $Y_{\text{OTs}}$ )

TFA (4.57) > water (4.0) > 97% HFIP (3.61) > HCOOH (3.04) > TFE (1.80) > CH<sub>3</sub>COOH (-0.61)

### The solvent as an electrophile

- Electrophilic attachment to the leaving group can assist its departure. (Analogous to silver + halides).
- Addition of small amounts of water increased the rate of alcoholysis of diphenylmethyl chloride, whilst the product remained almost entirely the corresponding ethyl ether.
- This effect is difficult to distinguish from ionizing ability.

Hammett *et al.* *JACS* **1937**, 59, 2542



### The solvent as a nucleophile

- $S_N1$ : rate-determining ionization step, nucleophilic solvent participation is absent.
- $S_N2$ : faster reaction with more nucleophilic solvent ( $Y$  kept constant).

Extended Grunwald-Winstein equation:

$$\log (k / k_0)_{\text{RX}} = mY + lN$$

$N$  is solvent nucleophilicity,  $l$  is sensitivity (in  $S_N1$   $l=0$ ).

Table IV. Minimum Estimates of Nucleophilic Solvent Assistance ( $k_s/k_c$ )<sup>a</sup>

Tosylates	Solvent								
	CF <sub>3</sub> CO <sub>2</sub> H	97 wt % (CF <sub>3</sub> ) <sub>2</sub> CHOH	97 wt % CF <sub>3</sub> CH <sub>2</sub> OH	HCO <sub>2</sub> H	70 wt % CF <sub>3</sub> CH <sub>2</sub> OH	AcOH	50% EtOH	80% EtOH	EtOH
2-Adamantyl <sup>b</sup>	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Pinacoyl <sup>d,e</sup>	1.0		3.6	2.4 <sup>f</sup>	3.2	8.6	9.5 <sup>f</sup>	12	
Cyclohexyl	1.0	0.62	3.2 <sup>g</sup>	5.0	6.6	78	61	11 <sup>h</sup>	286
Cyclopentyl	1.0			10		105		455	1680
4-Heptyl	1.0	0.87 <sup>g</sup>		3.9		28	46	146	
3-Pentyl	1.0	0.60 <sup>g</sup>		6.2		46	103	310	1310
2-Pentyl	1.0			9.6		88	195	616	
2-Butyl <sup>e</sup>	1.0		6.3	13	22	140	292	979	
2-Propyl <sup>e</sup>	1.0	0.57	15.3	32	57	472	1130	4430	23 500

Mayr *et al.* showed that HFIP/H<sub>2</sub>O mixtures are very strongly ionizing but essentially non-nucleophilic above 90% HFIP.

Schleyer *et al.* *JACS* **1976**, 98, 7667  
 Mayr *et al.* *J. Phys. Org. Chem.* **2013**, 26, 59

## Conclusions

- Extensively researched topic, many aspects are well understood but there is often confusion.
- Cl and Br as neighboring groups decrease the reaction rate (inductive effect) but give high stereospecificity (halonium) in most cases.
- External salts can have significant effect on reaction rates.
- Three main roles of solvent, these are quantifiable: ionizing medium, electrophile, nucleophile.