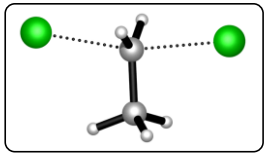
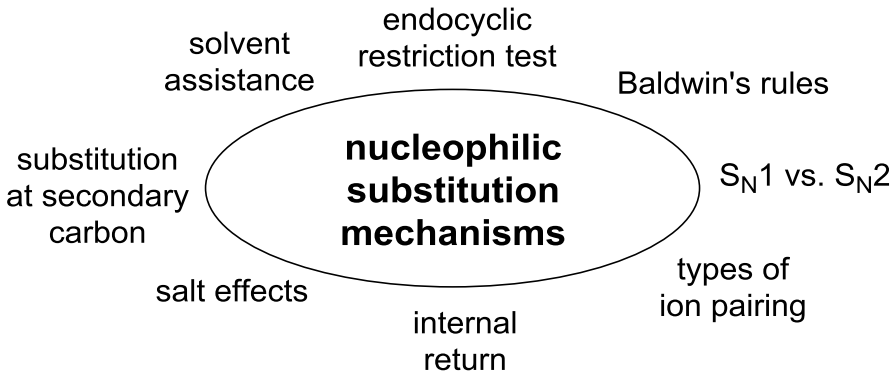
Nucleophilic Substitution Mechanisms

Eugene E. Kwan



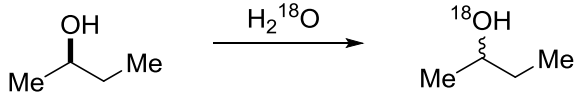
Scope of Lecture



Key Questions

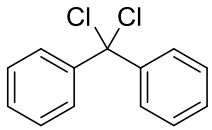
How can we explain the following?

(1)



$\mathbf{k_{racemization} = 2\ k_{exch}}$

(2)



\+

H_2O/acetone

$[Cl]_0$ (mM)	rate
0.80	4.71
5.88	3.91
26.20	2.45

Lecture notes edited by Richard Liu

Key References

(1) "Solvolytic Displacement Reactions." Streitwieser, A. McGraw-Hill, **1962**.

(2) "Solvolytic Substitution in Simple Alkyl Systems." Harris, J.M. *Progress in Physical Organic Chemistry*. **1974**, *11,* 89-173.

(3) "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.

(4) "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.

(5) "Dynamics for the Reactions of Ion Pair Intermediates of Solvolysis." Richard, J.P. *Advances in Physical Organic Chemistry.* **2004**, *39*, 1-26.

(6) "The Mechanisms of Nucleophilic Substitution in Aliphatic Compounds." Katritzky, A.R.; Brycki, B.E. *Chem. Soc. Rev.* **1990**, *19*, 83-105.

(7) "Secondary Hydrogen-Deuterium Isotope Effects and Transition State Structure in SN2 Processes." Westaway, K.C. Isotopes in Organic Chemistry. **1987**, Chapter 5, 275-392.

(8) "Using Kinetic Isotope Effects to Determine the Structure of the Transition States of SN2 Reactions." Westaway, K.C. *Advances in Physical Organic Chemistry*. **2006**, *41*, 217-273.

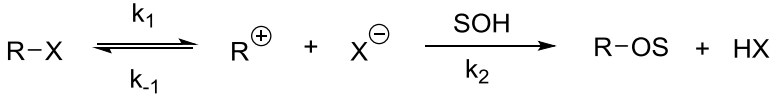
(9) "Secondary Deuterium Kinetic Isotope Effects and Transition State Structure." Matsson, O.; Westaway, K.C. *Advances in Physical Organic Chemistry.* **1999**, *31*, 143-248.

(10) "Secondary Deuterium-Isotope Effects on Reactions Proceeding Through Carbocations." Sunko, D.E.; Hehre, W.J. *Progress in Physical Organic Chemistry.* **1983**, *14*, 205-246

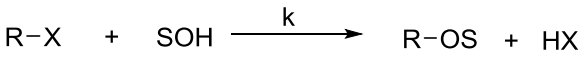
Introduction: The Hughes-Ingold Scheme

In sophomore organic chemistry, you probably encountered two limiting categories of mechanisms for substitution at aliphatic centers:

unimolecular (S_N1, A_N+D_N) *first-order overall if k_1 is rate-limiting*



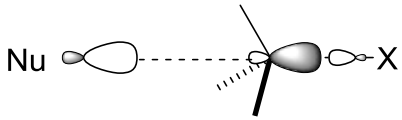
bimolecular (S_N2, A_ND_N) *second-order overall*



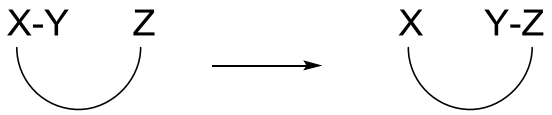
As we will see by the end of the lecture, this scheme is not adequate to describe many observations. We will focus our discussion key experiments that give insight into these mechanisms, as well as few applications.

The Endocyclic Restriction Test

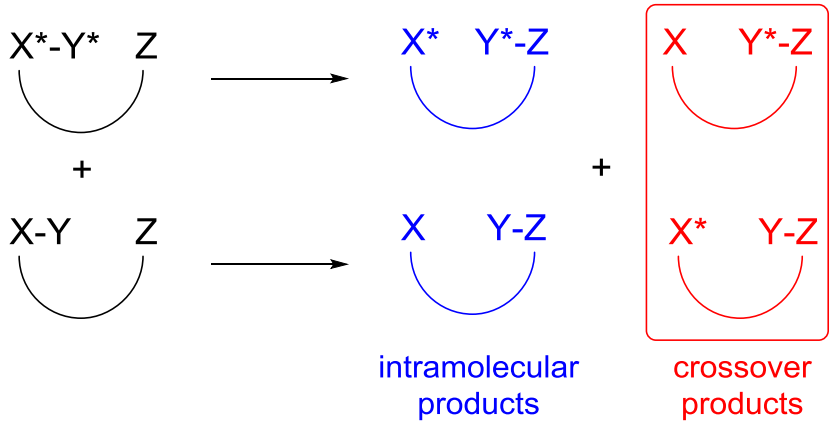
In S_N2 reactions, the optimal approach angle predicted by stereoelectronic considerations is 180°. How can we test this experimentally?



One way to examine this is the *endocyclic restriction test* (see Beak *Acc Chem Res* **1992** *25* 215-222):

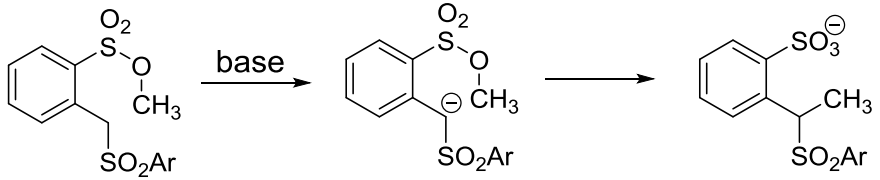


Of course, such a reaction could take place either *inter*- or *intra*-molecularly. How can these be distinguished?

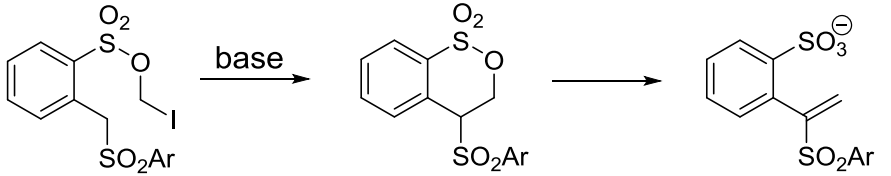


In a double-labelling experiment, both the molecule and the migrating group are labelled and mixed with unlabelled substrate. If the reaction is only intramolecular, then no singly-labeled crossover products will be formed.

For example, consider this base-promoted methyl transfer:



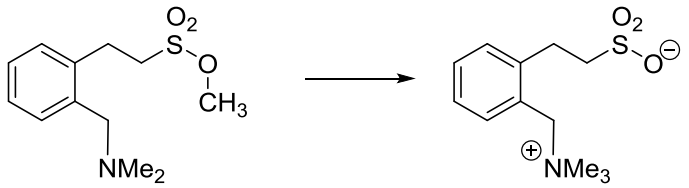
Crossover experiments show that the product is formed through a purely intermolecular process. This substrate cannot achieve the orbital overlap needed for reaction. In contrast, this one can:



intramolecular product only

Eschenmoser *Helv Chim Acta* **1970** *53* 2054

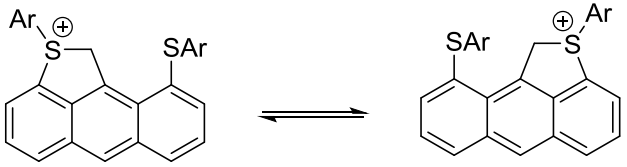
What is the effect of tether length? With a longer tether, the intramolecular process becomes somewhat more viable:



16% intramolecular

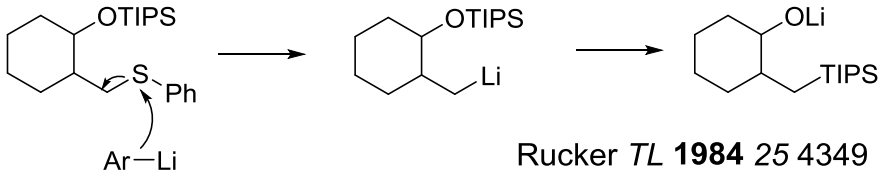
King *TL* **1982** *23* 4465

It has been estimated that a deviation of 17° away from linearity is allowed in this degenerate exchange:



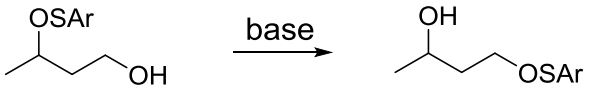
Substituent effects suggest that this is a rapid, intramolecular S_N2 reaction (Martin *JACS* **1973** *95* 2572).

Interestingly, these restrictions appear to be relaxed for third-row atoms like silicon, which have longer bonds and more diffuse orbitals:

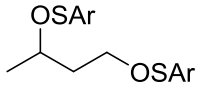


Rucker *TL* **1984** *25* 4349

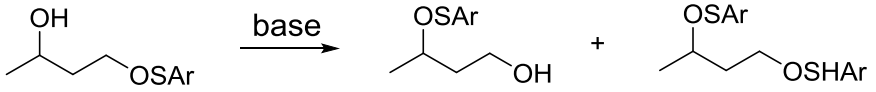
How would you determine if this reaction is intra- or inter-molecular?



In this case, labelling is not required, since product with two sulfurs would be expected in an intermolecular manifold:



As it turns out, this reaction is at least partly intermolecular, as the reaction is supressed by dilution. Furthermore, subjecting terminally sulfenated product to the reaction conditions results inboth secondary and doubly sulfenated material:



Aside: Baldwin's Rules

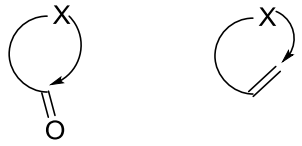
Baldwin has devised an empirical set of rules to allow one to determine if a certain ring closure will take place. All cyclizations are referred to as:

***n* - endo/exo - tet/trig/dig**

n: ring size being formed

exo/endo: whether the bond being broken is outside (exo) of or inside (endo) the ring

tet/trig/dig: whether the atom being attacked is tetrahedral (sp^3), trigonal (sp^2), or digonal (sp)



exo-trig **endo-trig**

Cyclizations are classified as **favored** or **disfavored**, rather than allowed or disallowed; the "rules" merely suggest whether a particular reaction would be facile or not.

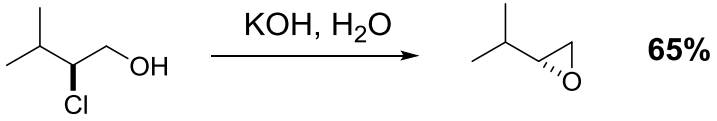
According to Baldwin (*Chem Comm* **1976** 734):

	EXO			ENDO		
	tet	**trig**	**dig**	**tet**	**trig**	**dig**
3	**yes**	**yes**	**no**	**no**	**no**	**no**
4	**yes**	**yes**	**no**	**no**	**no**	**no**
5	**yes**	**yes**	**yes**	**no**	**no**	**yes**
6	**yes**	**yes**	**yes**	**no**	**yes**	**yes**
7	**yes**	**yes**	**yes**	**no**	**yes**	**yes**

Evidently, the endo mode is much more restrictive than the exo mode, and sp electrophiles are more flexible than sp^3 ones. Here are some examples:

tet cyclizations

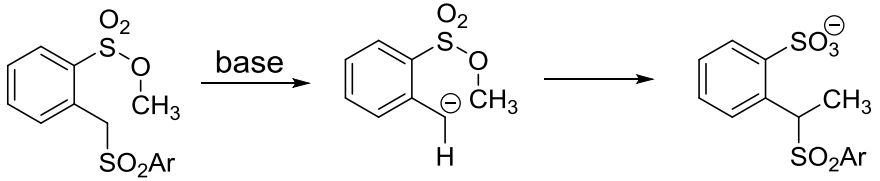
All exo-tet cyclizations are favored, but endo-tet cyclizations are generally disfavored unless the ring is very large (n>9).



65%

3-exo-tet: favored; a good method for epoxide synthesis

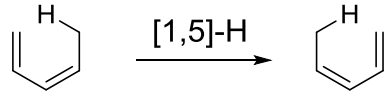
The methyl transfer from before is **6-endo-tet and disfavored**:



intermolecular process

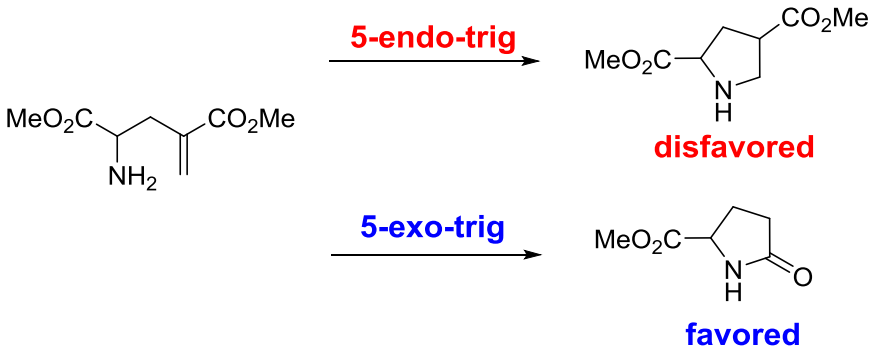
Baldwin's rules are generally good, but they are better in some instances than others. For instance, in reactions with larger atoms like silicon, they are frequently violated. They are exceptionally good in radical reactions.

Certainly, pericylic reactions do not obey Baldwin's Rules. 1,5-sigmatropic hydrogen shifts, for example, could be considered formally 6-endo-tet, but clearly occur:



trig cyclizations

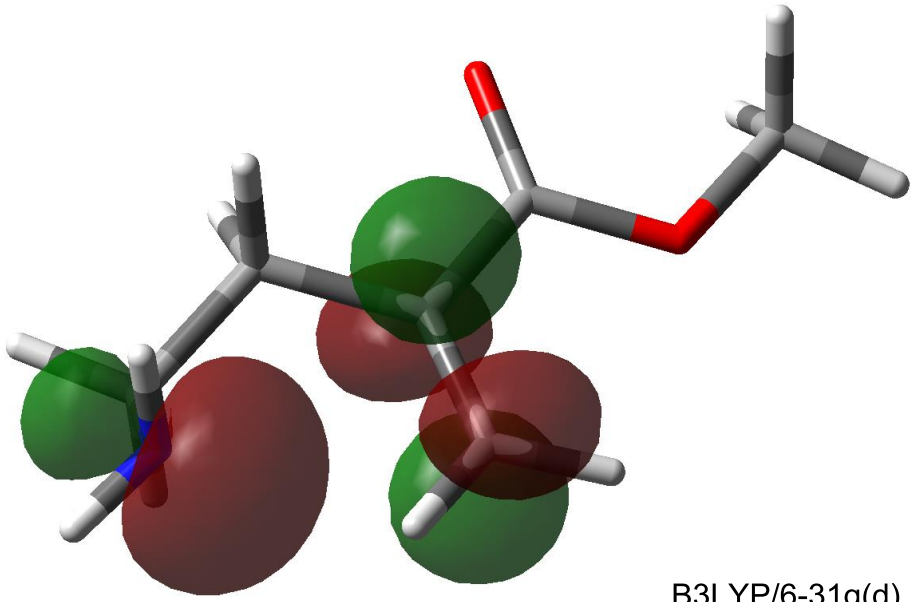
All exo-trig cyclizations are favored, but 5-endo-trig cyclizations and below are problematic. For example, this molecule has a choice between 5-exo-trig and 5-endo-trig pathways:



What is the donor-acceptor rationale for this behavior?

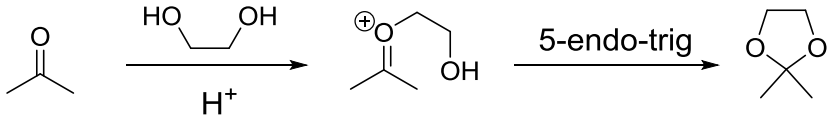
In the 5-endo-trig pathway, the amine lone pair must overlap with the π^* of the olefin. However, the five-membered ring prevents this. An illustration of this transition state is provided on the next page.

discussion and refs: March, 5th ed., pg 282-284
Dorwald, F.Z. Side Reactions in Organic Synthesis **2005**, Wiley-VCH, chapter 9.

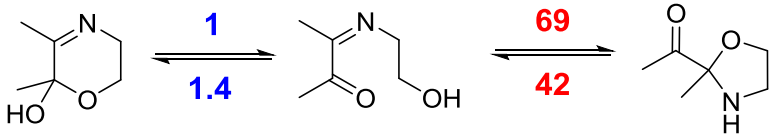


B3LYP/6-31g(d)

Attacks on oxocarbenium ions do not appear to follow the same rules. Ketalization reactions are clearly facile:



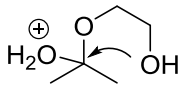
In fact, the rate constants for the ring-chain tautomerism of some oxazines in $CDCl_3$ have been determined by NMR (relative rates shown):



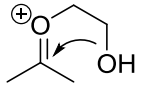
6-exo-trig **5-endo-trig**

Alcaide *JOC* **1992** *57* 2446

One plausible explanation is that addition occurs through an attack on a tetrahedral carbon, not a trigonal one!

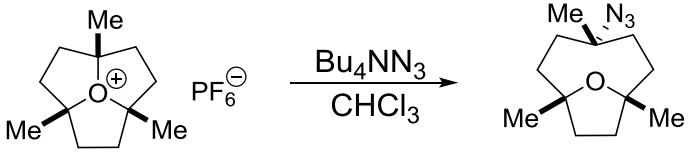


5-exo-tet



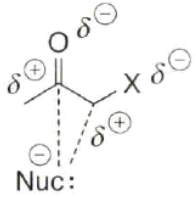
5-endo-trig

Although rare, S_N2 substitution at highly hindered carbons is known to be possible. For example, the following reaction uses a highly activated cationic leaving group:

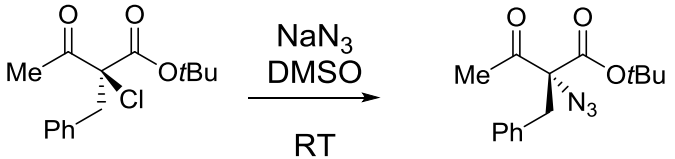


JACS **2010** *132* 10662

The most common examples involve centers that are adjacent to carbonyl(s). One proposal is that the polarization of the carbonyl enhances the overall electrophilicity of the electrophile:



Additionally, the electron-withdrawing carbonyl destabilizes any competing S_N1 pathways. Here is an example:



92% ee 89% yield, 92% ee

JACS **2012** *134* 9836

'Borderline' Mechanisms: Secondary Carbon Substitution

Despite the above examples, S_N2 at tertiary centers is quite rare, due to the stability of tertiary carbocations. But how about secondary substrates? Here are the possibilities:

(1) Only S_N2 is operative: rate = k_{SN2}[RX][Nuc]

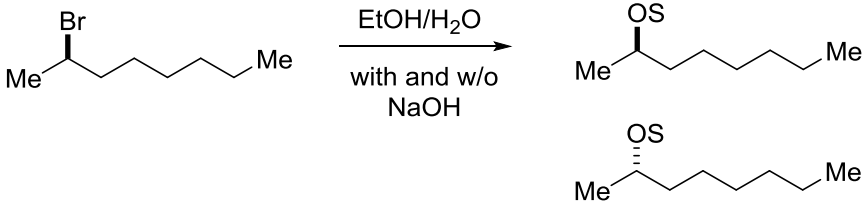
(2) Both S_N1 and S_N2 occur simultaneously:
rate = k_{SN1}[RX] + k_{SN2}[RX][Nuc]

(3) Another mechanism that is neither S_N1 nor S_N2 is operative.

In fact, this mechanism was the subject of intense debate. The Ingold textbook (1969) suggests possibility (2):

primary	80% S_N2
secondary	**45% S_N2**
tertiary	15% S_N2

Unfortunately, the evidence behind this claim is questionable. An early, misleading experiment, performed by Ingold and Hughes, involved the examination of the following solvolysis reaction with and without the addition of sodium hydroxide:



Reviews:
Murphy *J. Chem. Ed.* **2009** *86* 519
Raber and Harris *J. Chem. Ed.* **1972** *49* 60

Starting from enantiopure bromide, the authors report 65% ee in the product (a mixture of hydrolysis and ethanolysis products),

Hughes and Ingold concluded that simultaneous S_N1 and S_N2 pathways were operative. However, this conclusion is disputed because:

(1) The authors uncharacteristically neglect to provide many important experimental details in this report. For instance, the reported ee is apparently corrected for starting material racemization, but no details are given for the calculation!

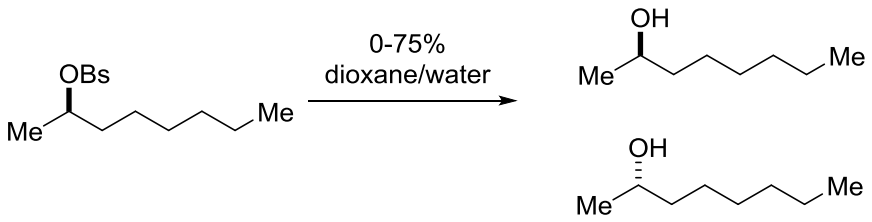
(2) The calculations are based on the assumption that without NaOH, the reaction is fully S_N1. This was based on the observation that the reaction exhibits first-order kinetics (actually, it's *pseudo*-first-order because of the large excess of nucleophile).

(3) The authors report that bromide produced during the reaction quickly racemizes any starting material through an S_N2 mechanism. However, not enough data was collected to properly quantify this.

(4) HBr, produced in the reaction, also racemizes the product alcohol. These reactions were run for more than 19 half-lives at elevated temperatures, so it is likely that this contributed to the observed loss in ee.

As a result of the experimental deficiencies here and some apparent contradictions in the follow-up papers, the proposed mixed mechanism was not conclusively demonstrated.

Here is a more conclusive experiment.
(Weiner and Sneen *JACS* **1965** *87* 287 & 292)



75-100% ee inversion

In this reaction, ee is inversely related to [dioxane]. Let's see what happens when the authors decided to try adding azide (a very good nucleophile) into the reaction.

Table I. Optical Purity of 2-Octanol and 2-Octyl Azide from the Solvolyses of 0.018 *M* 2-Octyl Brosylate in Aqueous Dioxane at 65° with Added Sodium Azide

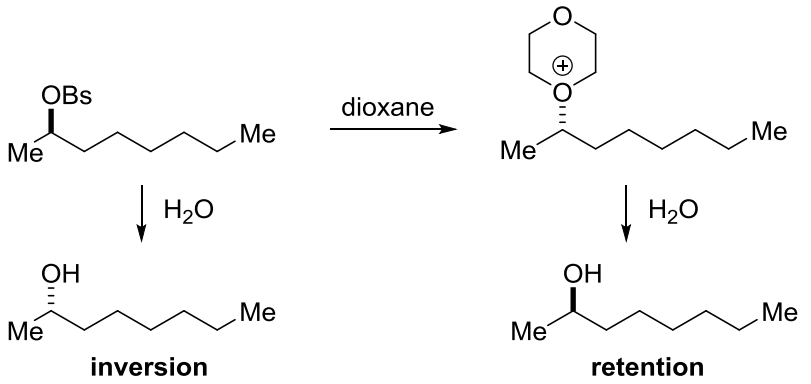
Solvent, % dioxane	$[NaN_3] \times 10^2$, *M*	2-Octanol, %	Optical purity of 2-octanol,[a] %	Optical purity of 2-octyl azide,[a] %
75	...	100	76.8	...
75	0.633	91.2	65.9	41.6
75	1.26	73.0	76.3	71.8
75	1.27	73.0	76.0	67.4
75	1.78	...	87.3	75.4
75	3.07	...	103	96.0
75	3.07	35.1	107	105
75	6.02	22.4	100	100
66.67	...	100	77.0	...
66.67	0.562	...	78.5	26.0
66.67	1.50	...	101	...
66.67	2.99	...	99.9	...
50[b]	...	100	87.5	...
50[b]	3.11	74.4	75.5	91.5
50[b]	9.30	48.2	95.6	91.5
25[b]	...	105	94.5	...
25[b]	3.26	83.0	96.4	80.0
25[b]	4.43	78.3	97.8	80.0
Water[c]	...	...	103	...
Water[c]	10.65	...	98.6	95.5

[a] Products were in all cases inverted. [b] 2-Octyl methanesulfonate (0.011–0.016 *M*) replaced the brosylate in these cases. [c] Methanesulfonate (0.0026–0.0052 *M*) replaced the brosylate.

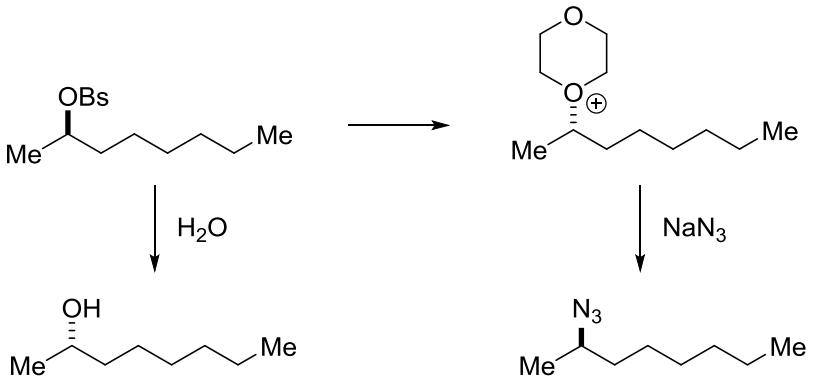
(1) As more azide was added, the ee of alcohol goes up.

(2) The ee of the azide product also goes up as the experimenters increase the concentration of azide ion.

How can we rationalize this? The authors propose that the observed 'racemization' is really competitive *double inversion*.

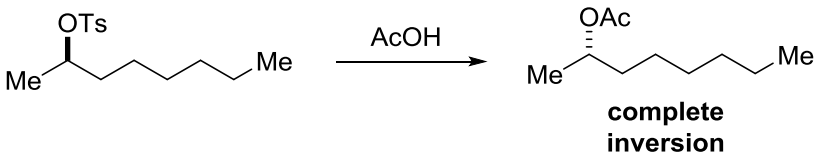


As more azide ion is added, more of the dioxane adduct is funneled to azide, and more of the alcohol is formed through the inversion pathway.



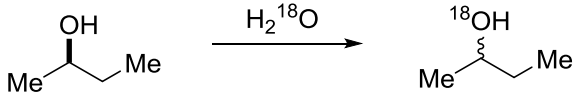
> "There is nothing borderline about the behavior of 2-octyl sulfonates, even in such highly ionizing solvents such as water. They undergo solvolysis by processes which are S_N2 in character. Apparent racemization is but the result of competitive but stereospecific displacement processes."

Here's some more evidence:



Streitwieser *TL* **1963** *4 27*

Even in very polar protic solvent, which prefers S_N1, full inversion is observed. Furthermore, in this labelling reaction, the rate constant of racemization is exactly half the rate constant of exchange.



$\mathbf{k_{racemization} = 2\ k_{exch}}$

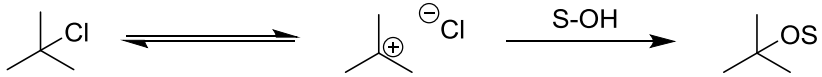
Bunton *J. Chem. Soc.* **1955** 604

Convince yourself that this is consistent with complete inversion at every substitution event.

Solvent Effects: The Schleyer System

We have seen that solvents can be important in these reactions. How can we investigate and quantify solvent effects?
(A detailed discussion can be found at "Medium Effects on the Rates and Mechanisms of Solvolytic Reactions."
Bentley, T.W.; Schleyer, P.v.R. *Adv. Phys. Org. Chem.* **1977** *14* 1.)

Consider the solvolysis of *tert*-butyl chloride. We might expect that more polar solvent systems might accelerate this reaction by promoting ionization.



We can quantify this effect using the Grunwald-Winstein equation:

$$\mathbf{Y = \log(k_{solvent}/k_{80\%\ EtOH})}$$

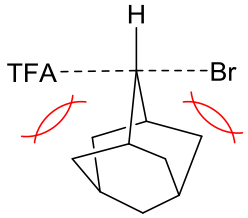
Here, Y is the *ionizing power* of the solvent, where the reference 80% EtOH/H_2O has Y = 0. Here are values for some other solvents:

Solvent	Y
water	3.493
ethanol	-2.033
methanol	-1.09
acetic acid	-1.639

We can apply this relationship to other systems, by introducing a factor *m*, which reflects the sensitivity of a reaction to solvent ionizing power, referenced to the *t*BuCl system (m = 1).

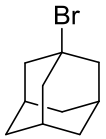
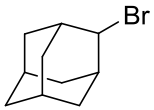
$$\mathbf{mY = \log(k_{solvent}/k_{80\%\ EtOH})}$$

It turns out that this is not the only solvent effect that is at work. Schleyer found that *nucleophilic solvent participation* can be important. As an example, he started by measuring the solvolysis rates of 1- and 2-adamantyl bromide. These reference reactions are assumed to reflect the intrinsic differencence between tertiary and secondary electrophiles *without* nucleophilic solvent participation. The idea is that trifluoroacetic acid is quite non-nucleophilic, and the adamantyl system is too hindered for solvent to attack:

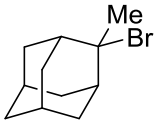


TS too crowded for solvent S_N2

Now let's consider some data:

in TFA:  *solvolyzes 3 x 10^7 times faster than* 

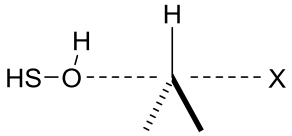
in 80% EtOH: *solvolyzes 5 x 10^3 times faster than*

solvolyzes at the same rate as 

(corrected for inductive effects)

As you can see, the difference between *t*-butyl bromide and isopropyl bromide is significantly less than the intrinsic tertiary vs secondary difference. Even taking Grunwald-Winstein solvent ionizing power into effect, there must be something else involved.

t-Butyl bromide solvolyzes at the same rate as a tertiary adamantyl system, so this additional effect must be affecting the isopropyl bromide only. This makes sense if we are looking for nucleophilic solvent participation.



Schleyer proposed a way to quantify nucleophilic solvent assistance:

$$\text{nucleophilic solvent assistance} = \frac{[\, k(\text{ROTs}) / k_t(\text{2-AdOTs}) \,]_{\text{any solvent}}}{[\, k(\text{ROTs}) / k_t(\text{2-AdOTs}) \,]_{\text{TFA}}}$$

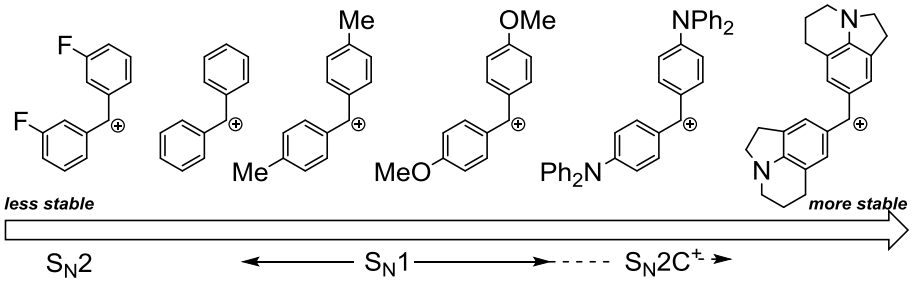
↑ non-nucleophilic

While S_N1 reactions have higher Grunwald-Winstein *m*, S_N2 reactions have more solvent assistance.

Rate-Determining Step in the S_N1/S_N2 Continuum

The unimolecular and bimolecular mechanisms are limiting cases in the Hughes-Ingold scheme. By carefully tuning the electrophile, we should be able to observe the change in kinetics as we move from one extreme to the other.

Mayr and coworkers devised the following set of experiments, wherein the solvolysis of benzhydryl bromides was shown to exhibit a continuum of kinetic behavior depending on stability of the carbocation that would result from heterolysis. I will explain in detail momentarily, but here is a summary:



1. no ionization
2. irreversible ionization
3. external return
4. rate-limiting solvolytic attack
5. persistent carbocation

Mayr *JACS* **2009** *131* 11392
Pure and Applied Chem. **2009** *81* 667

(1) Compounds on this extreme exhibit bimolecular kinetics only, since they only react by S_N2 mechanism.

(2) These compounds ionize, but are trapped so quickly there is never any return to starting material. Therefore, ionization is irreversible and rate-limiting.

(3) With these compounds, we observe external return of the anion. This means ionization is now reversible and on the timescale of solvolytic attack.

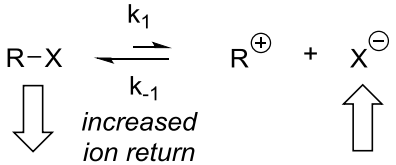
(4) These compounds form sufficiently stable carbocations that ***solvolytic attack is slow and rate-limiting.***

(5) Compounds on this extreme form such stable carbocations that they are never solvolyzed.

Note that ionization is not always rate-determining in S_N1!

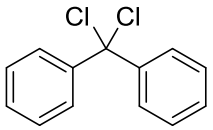
Common Ion Effects

Usually, however, carbocation trapping is fast, and the ionization is rate-determining. In these cases, we should expect common ion *rate depression*, since increasing the concentration of X^- should shift the ionization equilibrium to the left:



$$\text{rate} = \frac{k_1[RX]\,k_2[SOH]}{k_{-1}[X^-] + k_2[SOH]}$$

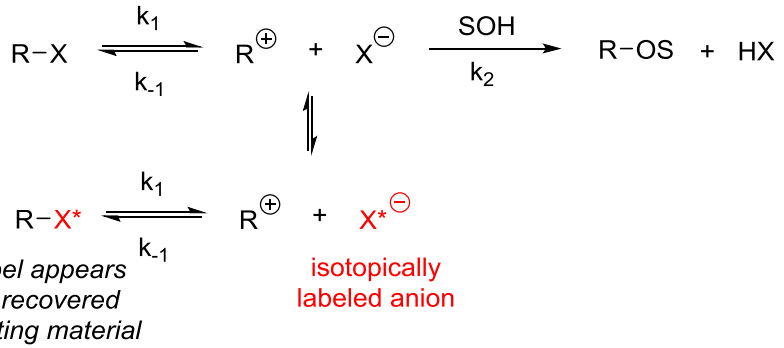
(We will learn how to derive these kinds of rate expression in a later lecture.) Indeed, these effects are frequently observed:



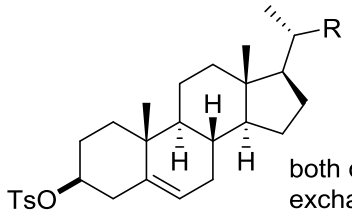
H_2O/acetone

$[Cl]_0$ (mM)	rate
0.80	4.71
5.88	3.91
26.20	2.45

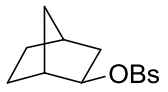
In these cases, since ionization is reversible, we should also expect common ion *exchange* if we use isotopically labelled ion:



Note that if the ion pair is extremely reactive we might not see exchange, because all cation is immediately partitioned to product. In this case, we shouldn't see depression either, since ion return is negligible. To summarize, in any given reaction we should expect to see *both* depression and exchange or *neither.*

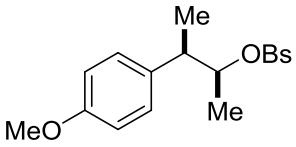


both depression and exchange observed



neither depression nor exchange observed

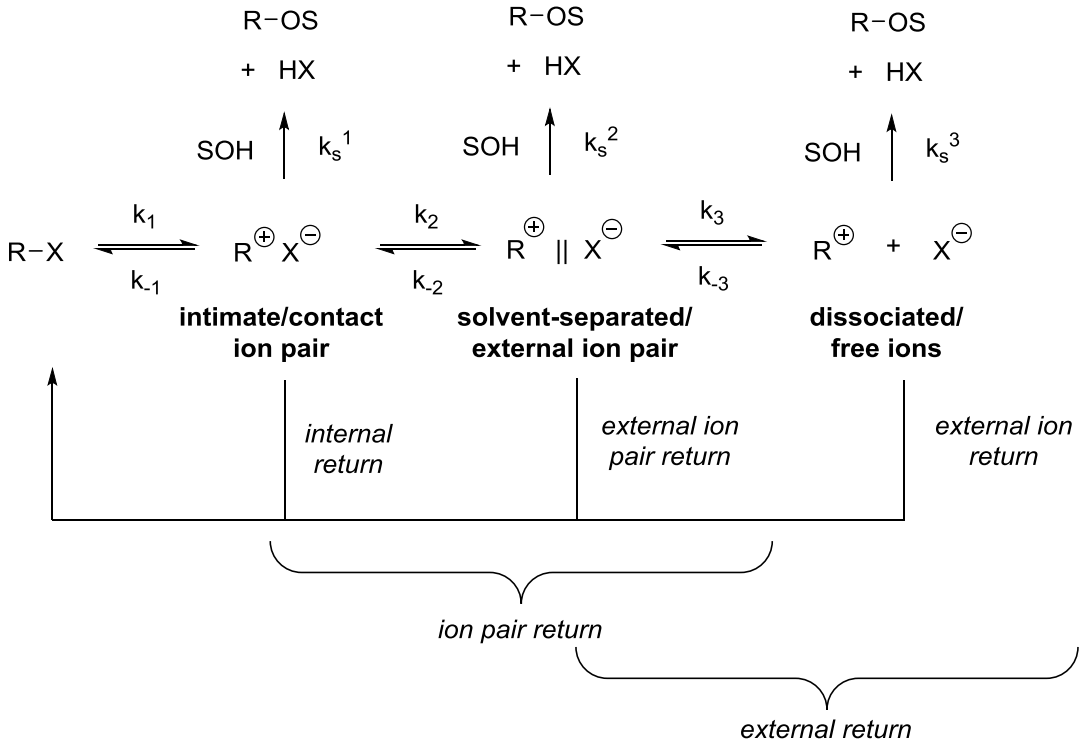
However, when we use a electrophile that is intermediate in reactivity, we encounter some anomalous behavior.



exchange observed,
but no depression

This cannot be rationalized under a Hughes-Ingold scheme. Winstein proposed a possible explanation: in addition to free ions, S_N1 reactions can proceed through several different types of ion pairs. We will explore this behavior in detail in the subsequent section.

Ion Pairing: the Winstein Model



A ***contact ion pair*** is the most closely associated type. Although we can consider the R-X bond to be broken, the only type of return is *internal*, in which the bond is reformed with the *same* X^-. Therefore, we cannot expect exchange or depression. Stereochemical information is also retained; we do not observe racemization.

Free ions, which are unassociated and behave as two different species in a rate law or equilibrium. Since the ions move independently, internal return is no longer possible, and we only have external return. In this case, we should expect both exchange and depression.

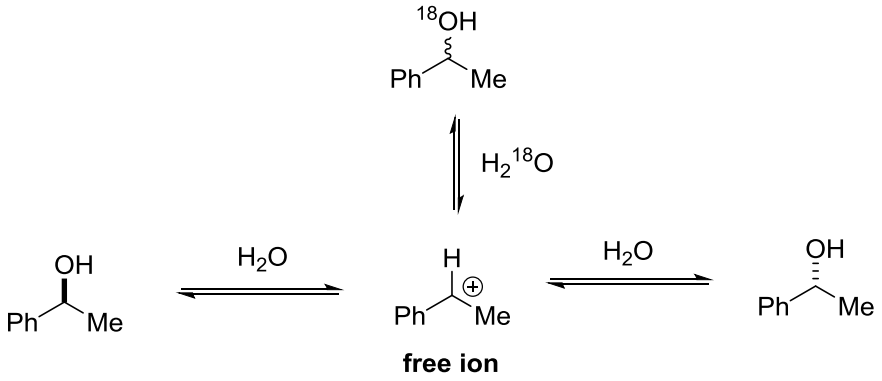
In a ***solvent-separated ion pair***, the ions are separated by several solvent molecules, but are still associated. In this case, it is possible to either reform the same R-X bond by internal return, but the species can also undergo *external* return, where R^+ reacts with a different, external X^-.

The anomalous case shown on the left is proposed to solvolyze through a solvent-separated ion pair. Since external return is possible, we see exchange. However, since no free ions are formed, we do not see depression.

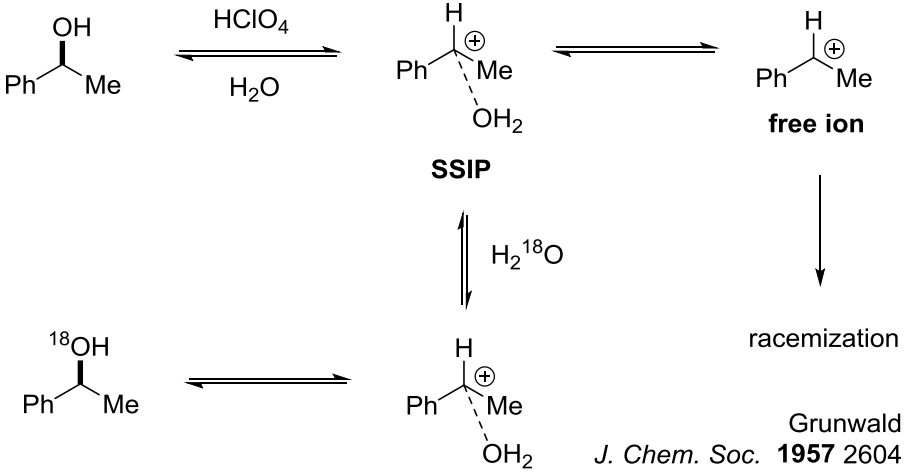
$R^{\oplus}$ || $X^{\ominus}$ is a single species in the rate law.

More Evidence for Solvent-Separated Ion Pairs

Consider the substitution reaction of 1-phenylethanol with labelled water under acidic conditions. If only free ions exist, every exchange event must proceed through free carbocation:



Therefore, we would expect $k_{exchange} = k_{rac}$ if we started with enantioenriched alcohol. In fact, we observe $k_{exchange}/k_{rac}$ = 0.82(4). This means some exchange events must occur *without racemization!* With solvent-separated ion pairs, external return can occur without racemization.



Grunwald *J. Chem. Soc.* **1957** 2604

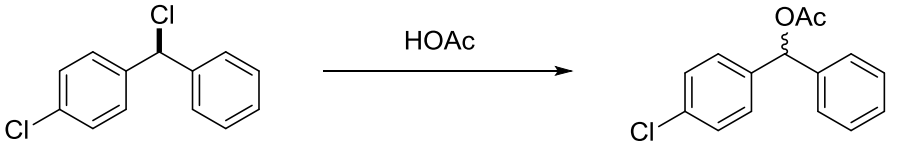
Evidence for Internal Return

How can we show that internal return occurs? First, we need to understand the difference between two important types of rate measurements:

Titrimetric rate measures the amount of one or more species. This can now be done by NMR, GC, IR, etc., but traditionally it was done by mass or by titration (we often generate HX).

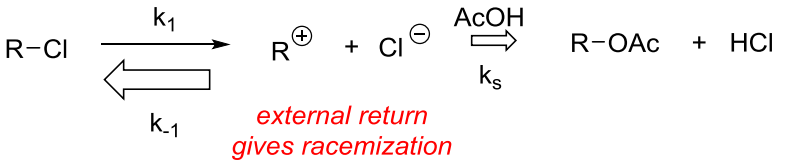
Polarimetric rate measures the optical rotation of the reaction mixture. In reactions of optically pure starting materials, polarimetric rate reflects the rate of ionization.

Winstein studied the following reaction:

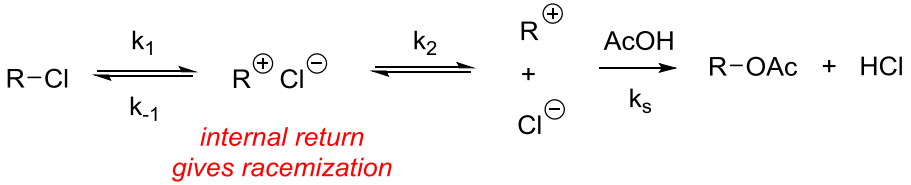


Remarkably, by comparing titrimetric and polarimetric rates, he found that racemization is 30-70 times faster than solvolysis! There are two mechanisms that would explain this:

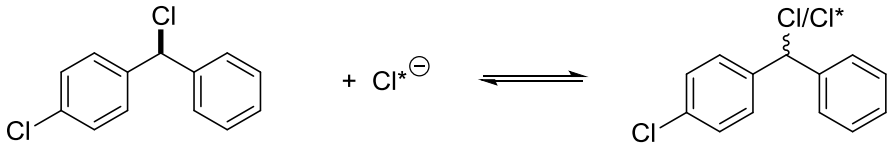
1) Hughes-Ingold mechanism with fast external return ($k_s << k_{-1}$)



2) Winstein mechanism with fast internal return ($k_2 << k_{-1}$)



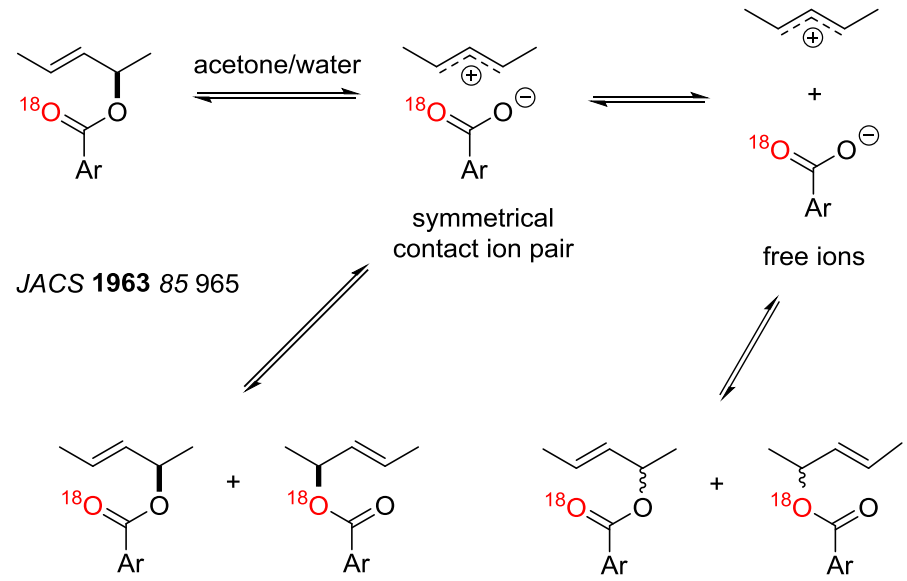
Fortunately, the two situations are easily distinguishable; we can easily measure the external return rate using a labelling experiment:



Winstein found that this rate was slower than the racemization rate, and concluded that there is indeed internal return.

More Evidence: Isotopic Scrambling in Symmetric Systems

In 1963, Goering performed a series of racemization/isotopic scrambling experiments on allyl esters with an ^{18}O labelled benzoate or tosylate leaving group. The idea was that free ion formation would result in both isotopic scrambling and loss of stereochemical information, while a contact ion pair mechanism would only scramble the isotopes.



By adding azide, the authors were able to suppress racemization, but full scrambling still occurred. How does this work? Apparently, azide only reacts with the free ion pair, but not the contact ion pair.

Special Salt Effects

Normally, S_N1 reactions are accelerated by increasing solvent polarity. One way to increase solvent polarity is by addition of an inorganic salt. We can define a *salt effect constant* b:

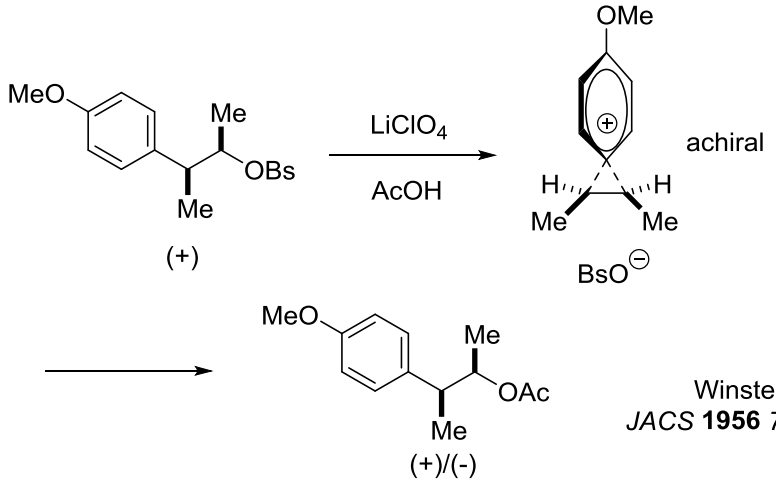
$$k = k_0 (1 + b [salt])$$

where k = rate constant with salt

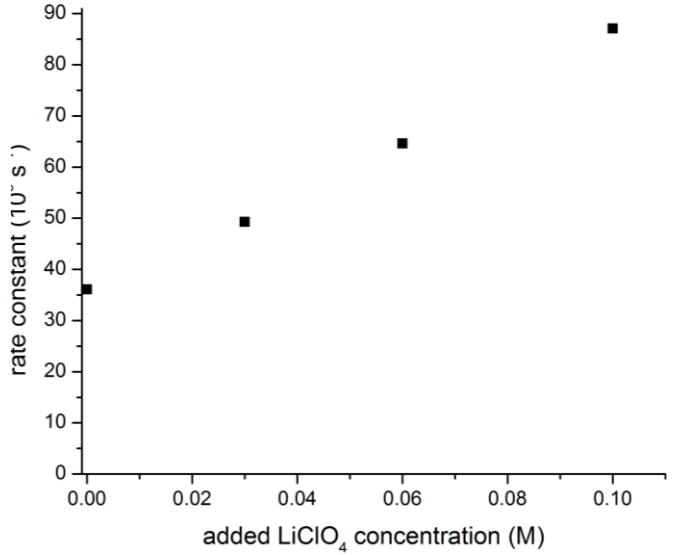
k_0 = rate constant without salt

(Note that in organic solvents, inorganic salts may be contact ion pairs. Thus, it has been suggested that perhaps $[salt]^{1/2}$ should be used instead, see Winstein *JACS* **1961** *83* 885.)

For instance, consider this solvolysis reaction performed under variable concentrations of added $LiClO_4$:



Winstein
JACS **1956** *78* 2780



Shown above is the polarimetric rate, or the rate of ionization, since the cation is *meso*. As expected increasing salt concentration promotes ionization in a linear manner. What about product formation? A plot of both polarimetric and titrimetric rates is displayed on the right.

(1) At low [salt], the rate greatly enhanced, but at high [salt], we observe only normal rate enhancement.

(2) The authors propose that $LiClO_4$ reacts with $R^+ \,||\, OBs^-$ to form $R^+ \,||\, ClO_4^-$ which cannot return.

(3) Once SSIP return is completely removed, only normal salt effect is apparent.

(4) The polarimetric rate still exceeds the titrimetric rate, so some return pathway is still operative, presumably from contact ion pair, which does not exchange with perchlorate.

(5) There is no common ion depression, so no free ions.

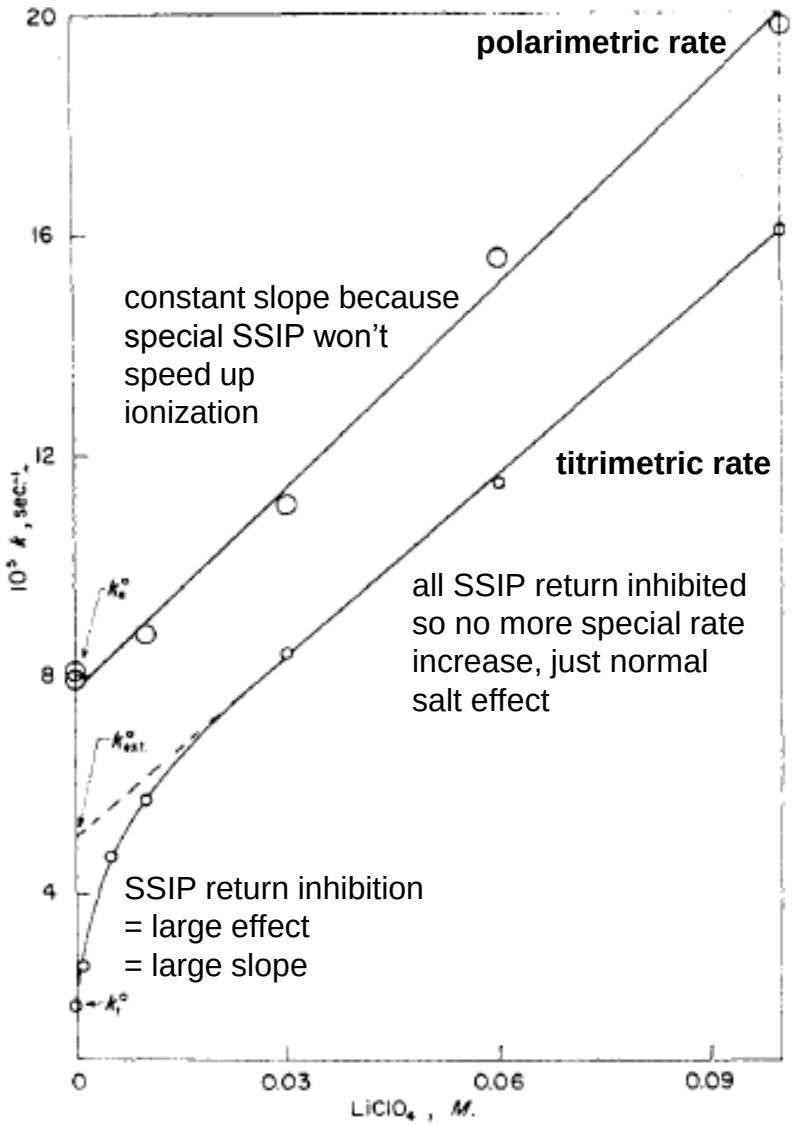
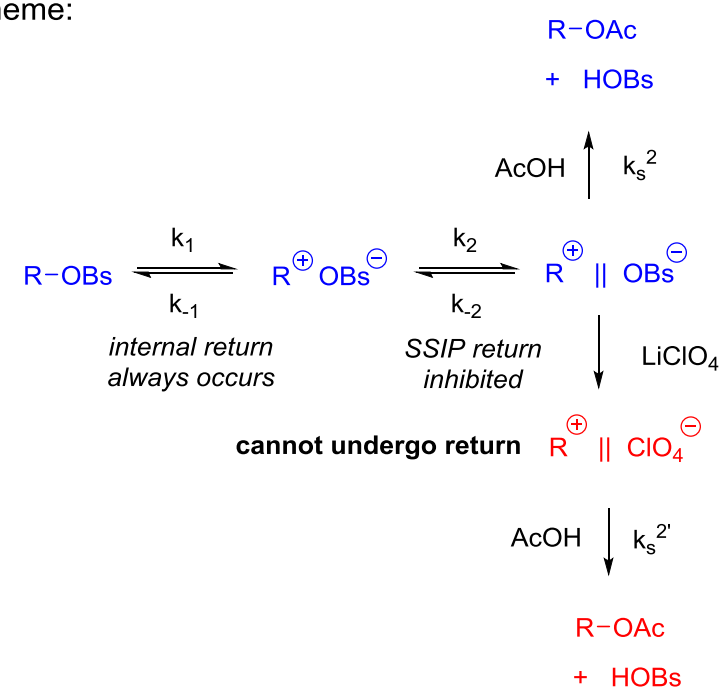


Fig. 2.—Effect of lithium perchlorate on acetolysis of *threo*-3-*p*-anisyl-2-butyl *p*-bromobenzenesulfonate at 25.0°.

To summarize, here is a scheme:

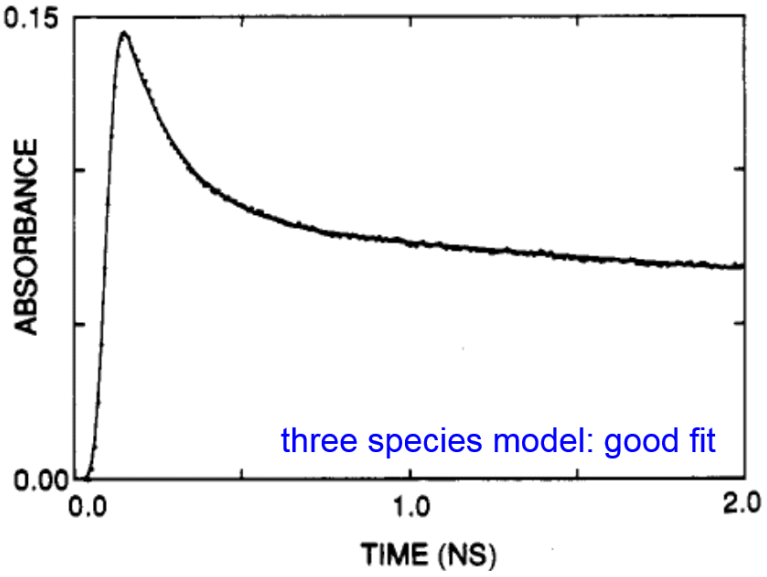


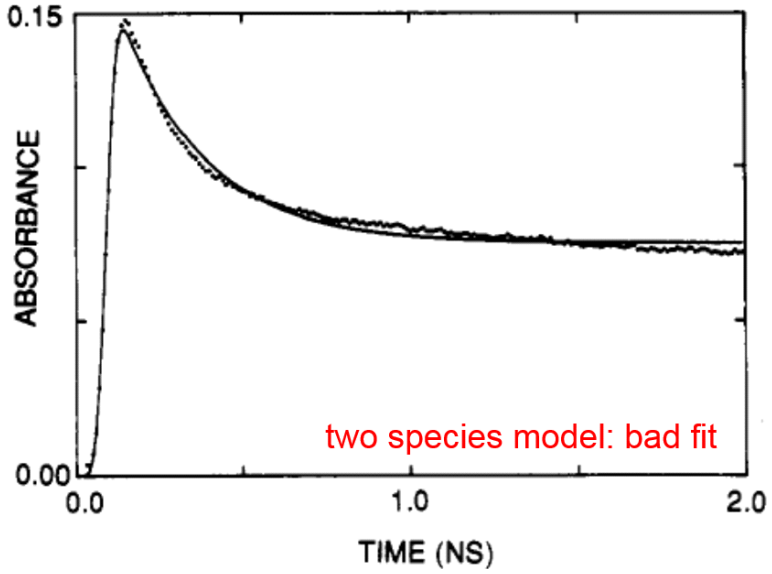
Winstein *JACS* **1954** *76* 2597
Winstein *JACS* **1958** *80* 169

Direct Observation of Ion Pairs

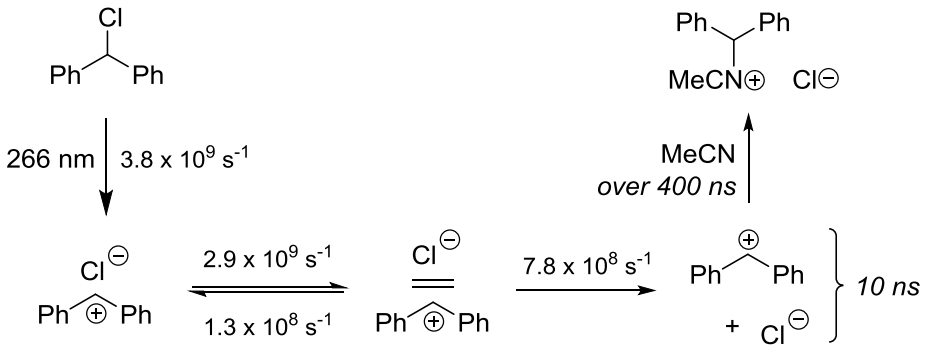
To conclude our discussion of ion pairing, here is a more modern experiment which uses flash photolysis to generate and *directly observe* these species (Peters *J. Phys. Chem.* **1994** *98* 401). The concept is simple: benzhydryl chloride is exposed to a brief flash of light, which ionizes it. The resulting ion pair species are monitored by absorption spectroscopy, and fitted to two types of kinetic models:

(1) a two species model: CIP, free ions
(2) a three species model: CIP, SSIP, free ions





Clearly, the three species model fits very well. In fact, the individual rate constants have been calculated.

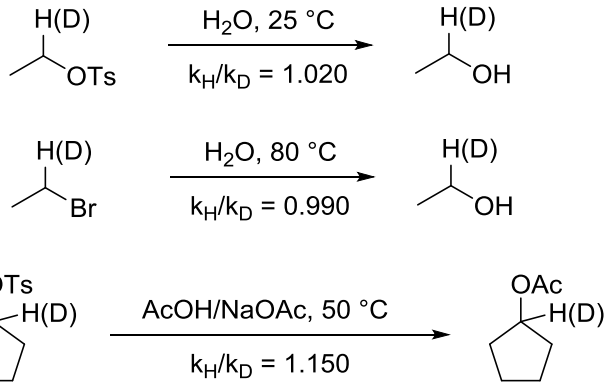


Kinetic Isotope Effects

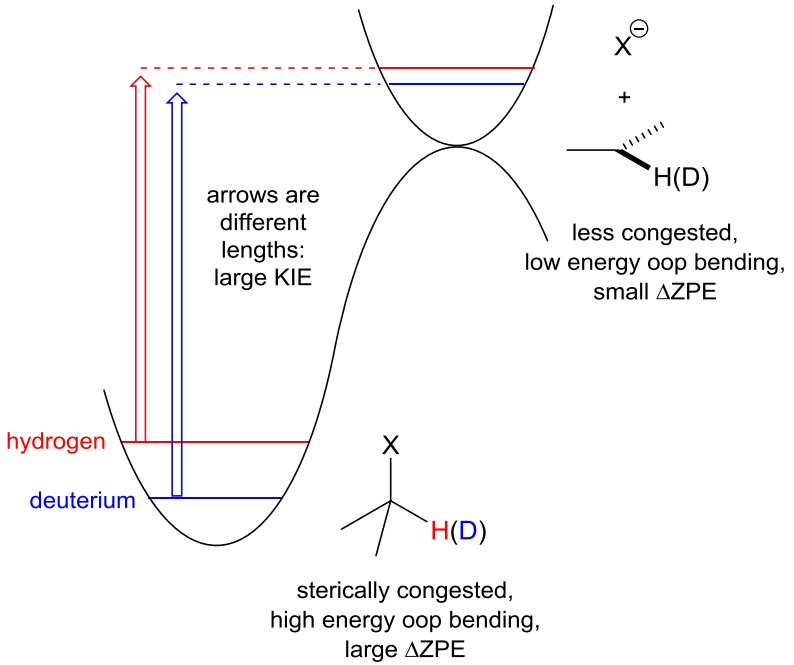
Can the α-H/D secondary kinetic isotope effect distinguish S_N1 pathways from S_N2? Recall the Streitweiser model, which relates this isotope effect to the change in zero-point energy of out-of-plane bending between ground and transition states.

Commonly, it is claimed that KIE > 1.07 means S_N1, while KIE < 1.05 means S_N2. This rule is **heavily** disputed. A more conservative interpretation is that the KIE reflects the 'looseness' of the transition state.

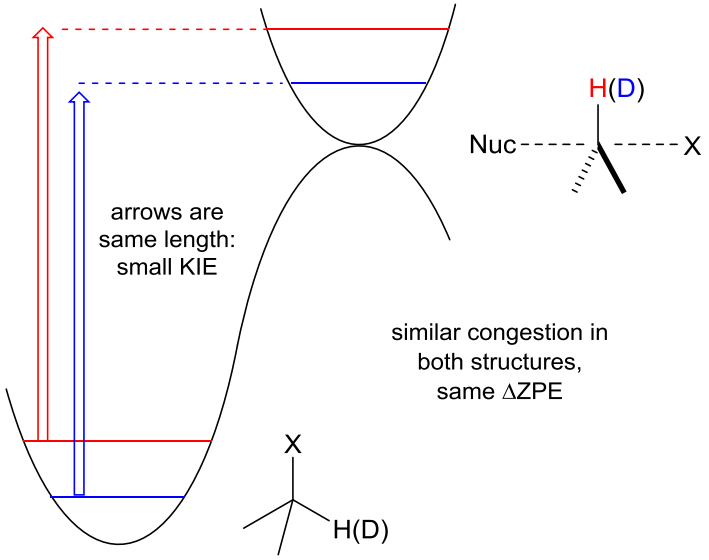
Here's some examples:



S_N1 mechanism

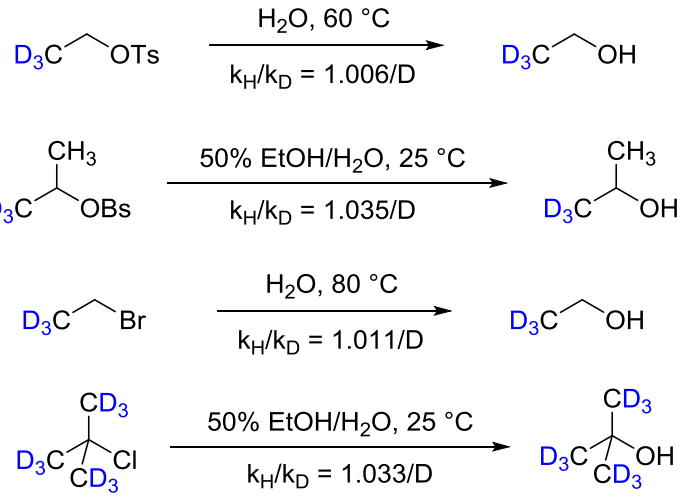


S_N2 mechanism

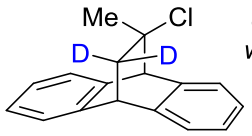


β-Deuterium Substitution

These KIEs arise primarily because of hyperconjugation, since C-H bonds are better donors than C-D. Therefore, the β-H/D KIE measures transition state charge buildup.

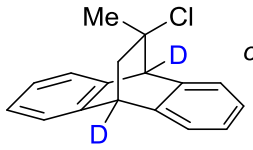


As you can see these KIEs are usually normal, and larger for S_N1 reactions. Since the main origin of the effect is hyperconjugation, the KIE is also sensitive to dihedral angle in rigid systems.



can overlap with p-orbital in cation

k_H/k_D = 1.07 per D



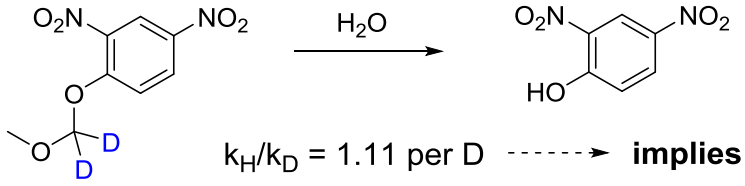
orthogonal

k_H/k_D = 0.99 per D

Shiner *JACS* **1965** *87* 1382

Limitations of KIE Experiments

Kinetic isotope effects should not be used alone. Here is an example where they seem to contradict other experiments. Consider the solvolysis of this 2,4-DNP acetal:



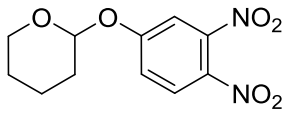
k_H/k_D = 1.11 per D ⇢ **implies S_N1**

Kirby *JCS PT2* **1978** 357

All other experiments strongly suggest an S_N2 mechanism:

(1) negative entropy of activation:

$\Delta S^{\ddagger}$ = – 7 e.u. for this reaction. One can compare this with a similar system which almost certainly undergoes S_N1: $\Delta S^{\ddagger}$ = +2 e.u. for



THP acetal
(hydrolyzed 10^3-10^4x faster)

(2) insensitive to solvent effects

The Grunwald-Winstein constant *m* measures the sensitivity of a reaction to solvent polarity, referenced to solvolysis of *t*BuCl in 80% EtOH/H_2O (*m* = 1). For this reaction, *m* = 0.29 (vs. 0.77 for THP acetal).

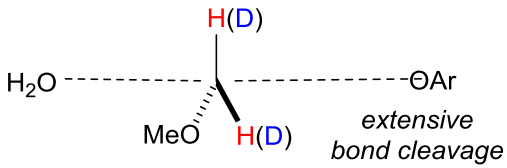
(3) negative salt effect

S_N1 reactions usually have positive salt effects.

Why should an S_N2 mechanism operate here when the THP acetal undergoes S_N1 hydrolysis?

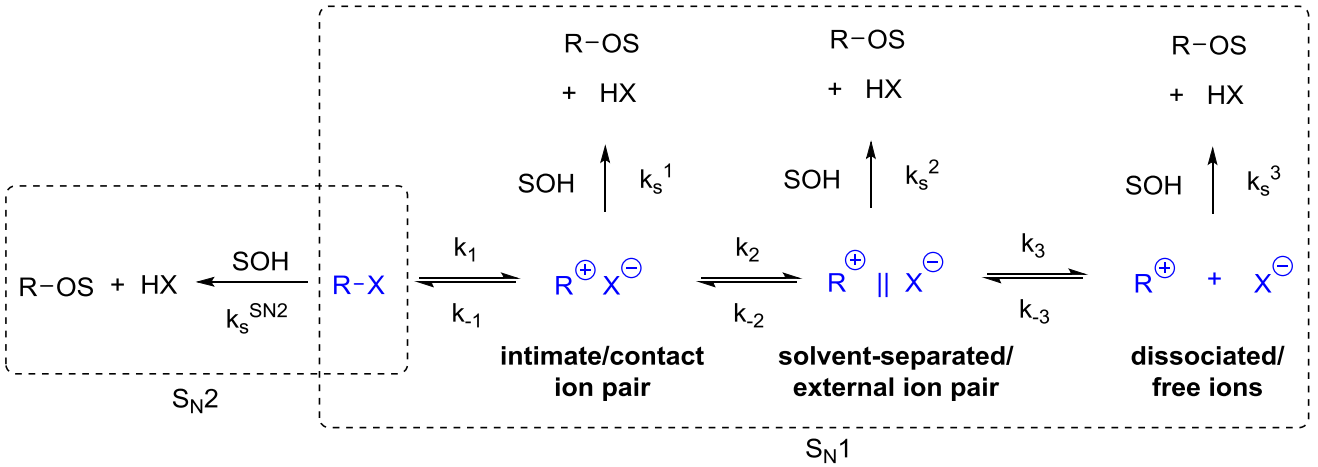
One suggestion is that this is a far less hindered electrophile than the THP acetal. Furthermore, endocyclic oxocarbenium ions are typically much more stable than acyclic ones. Regardless, we still need to explain the high KIE.

The proposed rationale is that the stabilization of the S_N2 transition state by the adjacent oxygen allows for a very loose geometry where the C-OAr bond is mostly disconnected. Furthermore, this reaction has been observed to be much less sensitive to nucleophile basicity than typical S_N2 reactions, perhaps as a result of week C-Nu interaction in the loose transition state.



Regardless, it is clear that there is no hard and fast rule that reliably translates KIEs into mechanism.

Summary



- Secondary alkyl electrophiles solvolyze by an invertive, asynchronous S_N2 mechanism.

- S_N1 and S_N2 manifolds generally do not overlap.

- S_N1 reactions involve many differentially dissociated ion pairs.

- Ionization is not always rate-determining.

- S_N2 reactions are assisted by nucleophilic solvent.

- Kinetic isotope effects should be interpreted cautiously.