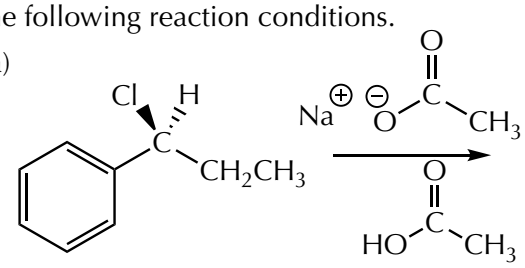
Thinking in Blue #10 - This question appeared on an exam in 2003. It is not in the book.

Predict the main product or products, as directed, from (*S*)-1-chloro-1-phenylpropane under the following reaction conditions.

(a)



a single major product

(b) If dimethylsulfoxide (DMSO) is used as the solvent in (a), the reaction is predicted to be:

(circle one:)
faster
unaffected
slower

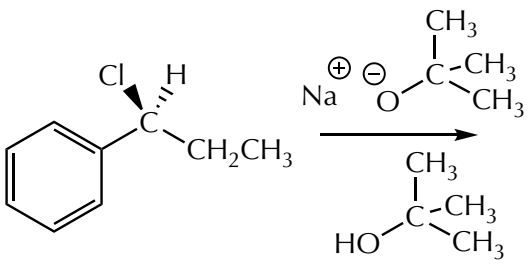
(c) If (*S*)-1-bromo-1-phenylpropane was used in (a), the reaction is predicted to be:

(circle one:)
faster
unaffected
slower

(d) If (*S*)-1-chloro-2-methyl-1-phenylpropane was used in (a), the reaction is predicted to be:

(circle one:)
faster
unaffected
slower

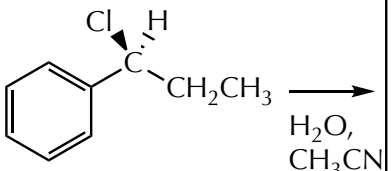
(e)



the more stable of two major products

(f) If (*S*)-1-chloro-1-phenylethane was used in (e), there is only 1 major product instead of two of them; briefly explain why.

(g)



one of two stereoisomeric products containing oxygen

+

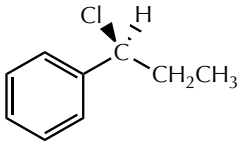
one of two stereoisomeric products containing oxygen

treatment with aqueous acid

isomerization via carbocation rearrangement

(h) When the two products that form in (g) are heated for an extended time in a strong aqueous acid solution, they both undergo an isomerization to give a single compound with the same molecular formula as the products in (g), and whose mechanism of formation proceeds through carbocation rearrangement. What is the structure of this isomerized product?

Predict the main product or products, as directed, from (*S*)-1-chloro-1-phenylpropane under the following reaction conditions.

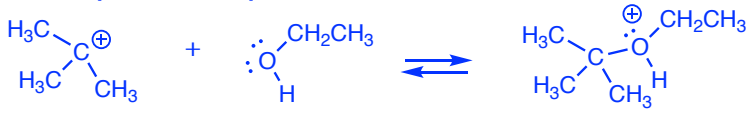


To repeat from the previous question (*Thinking in Blue,* Question 9):

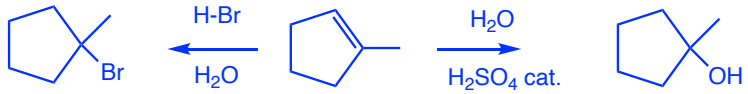
"In the early stages of learning reaction chemistry, the fact that there are actually only a few fundamental classifications of chemical reactions is the most useful information. With only a few different kinds of bonds to deal with (sigma and pi), it is simply not surprising that the four fundamental types of reactions involve a change in connectivity between sigma and pi bonds"… complexation/decomplexation, addition, substitution, and elimination.

At this point, there are examples in each category, so there are more choices for "predicting products from reactions."

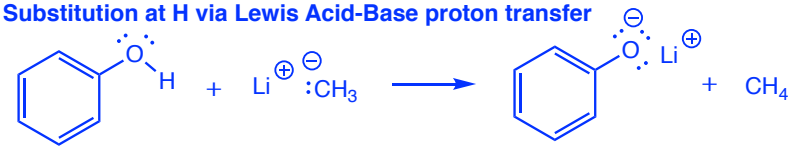
Complexation/decomplexation of open shell atoms with Lewis bases



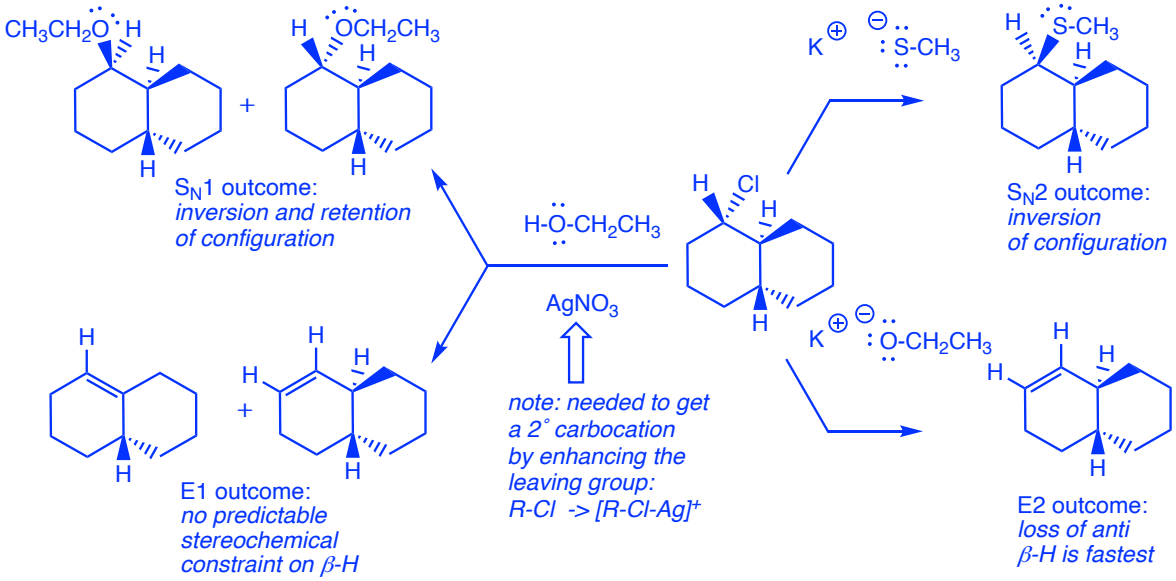
Electrophilic Addition of strong and weak Bronsted acids to CC pi bonds



Nucleophilic Substitution at H via Lewis Acid-Base proton transfer



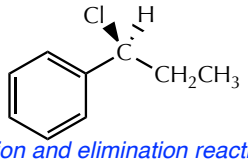
Nucleophilic Substitution and/or Elimination at sp^3 C-Leaving Group with Lewis/Bronsted Bases (bimolecular options S_N2 and/or E2; unimolecular S_N1 and/or E1)



The total outcome from the unimolecular pathways (S_N1 + E1) is exactly the same as the more generic analysis of all possible outcomes from substitution and elimination (see previous *Thinking in Blue*, Question 9), where you would have said that there were 4 possible outcomes. If S_N2 is anticipated, then you see just the substitution product with inversion; and if E2 is anticipated, there is a preference for the loss of anti β-Hs to the leaving group.

It is an important insight to understand that the analysis for the possible substitution and elimination reaction products does not change. Once you have a way to predict the most likely mechanistic pathway, then you can make a specific prediction about a reaction outcome.

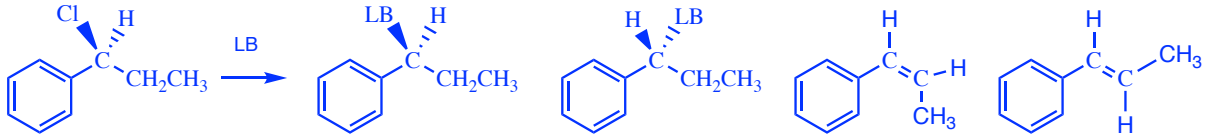
Predict the main product or products, as directed, from (*S*)-1-chloro-1-phenylpropane under the following reaction conditions.



This is worth repeating:

It is an important insight to understand that the analysis for the possible substitution and elimination reaction products does not change. Once you have a way to predict the most likely mechanistic pathway, then you can make a specific prediction about a reaction outcome.

So, for this molecule, long before considering the details of this question, the analysis of possible substitution and elimination outcomes can be done, because regardless of the specifics, these are the only possible products, and a predictive only serves to narrow down the options. This molecule has a leaving group associated with a stereocenter, so there are two possible S_N products (retention and inversion). There are two β-Hs on the "CH_2" group, and none elsewhere; a double bond located there has both (*E*) and (*Z*) diastereomers. There are four possible outcomes from substitution and elimination.

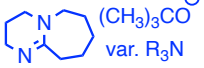


A predictive model only yields the anticipated pathway. The concepts from the pathway must be applied to the specific case to get a final answer to the question.

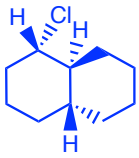
Predicting which substitution or elimination pathway is favored appears complex because the decision is not binary, it is multi-conditional. A binary decision is based on a single condition (If… A, then… G), e.g., If the molecule has one asymmetric tetrahedral stereocenter, then it will have two chiral stereoisomers that are enantiomers of one another. A multi-conditional decision, as the name implied, depends on combinations of factors (If A & B & D, then R; but if A & C & D, then M), e.g., If it is the right Monday (Sept-Dec) and it is 8 AM and you are awake, then you can attend CHEM 210; If it is Tuesday and it is 8AM and you are awake, then you cannot.

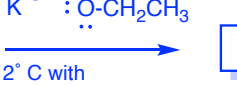
The prediction of which substitution or elimination pathway is favored is multi-conditional. The decision depends on:
(a) whether an sp^3 C-LG bond is present
(b) whether a Lewis basic partner is present
(c) the degree of substitution of the C with the LG
(d) the nature of the Lewis basic partner (charge, pK_a of its conjugate acid, hindrance)
(e) the ability of the C with the LG to support a carbocation
(f) reaction conditions that can support a carbocation

the proper prediction is only the diagnosis - you must then know how to apply that idea to the specific case

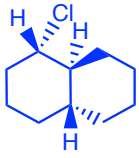
if LB is…	poor Bronsted base	moderate Bronsted base	good Bronsted base	if LB is none of these	
	unhindered anion w/conj acid pKa < 15; or uncharged sp^3 N,P,S	unhindered anion w/conj acid pKa 15-30	conj acid pKa > 30; or hindered bases conj acid pKa > 10 	***and*** if polar medium (protic: H_2O, ROH, RCO_2H; aprotic: DMSO, DMF, HMPA) ***and***…	
if sp^3 C-LG is…				non-res stab C+	res-stab C+
1˚C, incl. unhindered no β-H	S$_N$2	S$_N$2	S$_N$2 (unhind, no β-H) E2 (β-H)	NR	S$_N$1/E1
2˚C	S$_N$2	E2 (β-H)	E2 (β-H)	NR	
3˚C	no S$_N$2 no E2	E2 (β-H)	E2 (β-H)	S$_N$1/E1	

from the prior page:





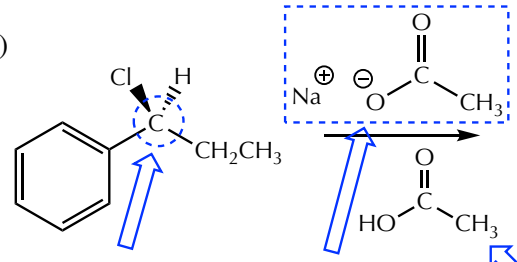
2˚ C with moderate Bronsted base → E2 (β-H)



2˚ C; no good base; polar solvent; not a good C^+ without Ag^+ to help → NR w/o $AgNO_3$; S$_N$1/E1 w/ $AgNO_3$

Predict the main product or products, as directed, from (*S*)-1-chloro-1-phenylpropane under the following reaction conditions.

(a)



a single major product

see general analysis of this structure on previous page; this is useful information!

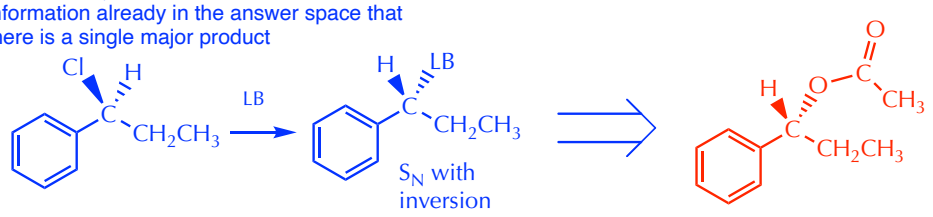
S_N2 gives one outcome
E2 gives two outcomes
S_N1/E1 gives four outcomes

the sp^3 C-LG is…
2° with the possibility for resonance delocalization in a carbocation here

LB is…
poor Bronsted base
unhindered anion
w/conj acid $pK_a < 15$;
(here, pK_a is 4.8)

the solvent is given but does not play a role in the decision-making here; the analysis for predicting the reaction follows a sequence, and when the bimolecular reaction is anticipated, the outcome does not use solvent as a criterion

this combination predicts S_N2 (S_N inversion) as the outcome, and that is consistent with the information already in the answer space that there is a single major product



Parts (b)-(d) stand out immediately as relative rate problems (the choices involve anticipating if the reaction is faster, slower, or unaffected upon making a change. Such changes need to be highly controlled, that is, only one change can be made with respect to the reference reaction (above). You can change solvent, concentration, and structure of the reagents. The general trends cannot be deduced from the information presented; you need to understand them, identify them, and apply them.

(b) If dimethylsulfoxide (DMSO) is used as the solvent in (a), the reaction is predicted to be:

(circle one:)
faster
unaffected
slower

Two broad generalizations apply to solvent effects in S_N/E reactions in CHEM 210: (1) a polar solvent is one of the three criteria for getting carbocation formation, and (2) all else equal, reactions in polar aprotic solvents (DMSO, DMF, HMPA) are faster than the polar protic counterparts (protic solvents hydrogen bond with Lewis bases, particularly ions, and stabilize them, thereby increasing the activation energy for their reactions.

(b) If dimethylsulfoxide (DMSO) is used as the solvent in (a), the reaction is predicted to be:

(circle one:)
faster
unaffected
slower

(c) If (*S*)-1-bromo-1-phenylpropane was used in (a), the reaction is predicted to be:

(circle one:)
faster
unaffected
slower

As with changing the solvent (part b), any correlation with structural variation needs to be done by holding all else equal. Here, the leaving group is changed from a chlorine to a bromine atom. Leaving group ability, in general, follows Bronsted base strength: the weaker the base, the better it was as a leaving group because it's not sharing its electrons in the bond to carbon as well as a stronger base. The generalization is quite limited because the comparisons need to be as direct as possible. Bromide is a weaker base than chloride, and the atom-size difference makes the C -Br bond break faster than C-Cl.

(c) If (*S*)-1-bromo-1-phenylpropane was used in (a), the reaction is predicted to be:

(circle one:)
faster
unaffected
slower

(d) If (*S*)-1-chloro-2-methyl-1-phenylpropane was used in (a), the reaction is predicted to be:

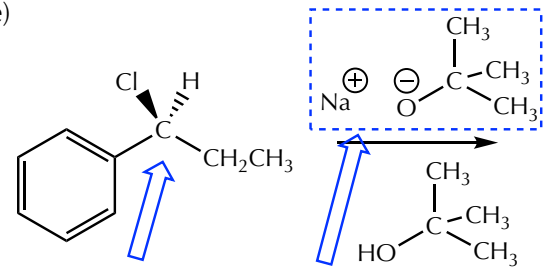
(circle one:)
faster
unaffected
slower

Here, the structural variation is in the electrophile. The molecule in part (d) has an extra methyl group on the β-carbon, and S_N2 reactions are sensitive to crowding (steric hindrance) of any kind because a direct collision with the carbon atom bearing the leaving group needs to take place. A more crowded Lewis base or a more crowded C-LG bond will, all else equal, make the transition state energy higher and slow the reaction.

(d) If (*S*)-1-chloro-2-methyl-1-phenylpropane was used in (a), the reaction is predicted to be:

(circle one:)
faster
unaffected
slower

(e)



the more stable of two major products

see general analysis of this structure on the earlier page; this is (again) useful information!

S_N2 gives one outcome
E2 gives two outcomes
S_N1/E1 gives four outcomes

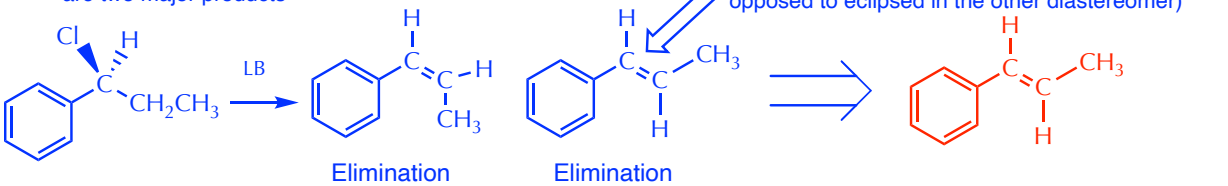
the sp^3 C-LG is (still)…
2˚with the possibility for resonance delocalization in a carbocation here

LB is…
hindered anion w/conj acid pK_a > 10; (here, pK_a is 16-17)

the solvent is given (again) but does not play a role in the decision-making here; the analysis for predicting the reaction follows a sequence, and when the bimolecular reaction is anticipated, the outcome does not use solvent as a criterion

this combination predicts E2 (anti β-H elimination) as the outcome, and that is consistent with the information already in the answer space that there are two major products

The (*E*)-isomer is more stable than the (*Z*)-isomer because there is less steric hindrance between the phenyl and methyl groups (which are anti, here, as opposed to eclipsed in the other diastereomer)



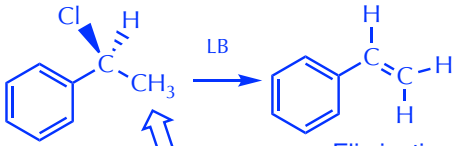
Elimination (*Z*)-isomer

Elimination (*E*)-isomer

These exact product structures were already anticipated in the original analysis. The only real question, based on the information provided, was which outcome was required. First, that it was the E2 elimination, and second, that the two products needed to be assessed for their relative stability.

(f) If (*S*)-1-chloro-1-phenylethane was used in (e), there is only 1 major product instead of two of them; briefly explain why.

The text references a change in the structure of the electrophile in part (e): the ethyl group is changed to a methyl group. A specific outcome is cited: there is only one major product instead of two, and the question is why?

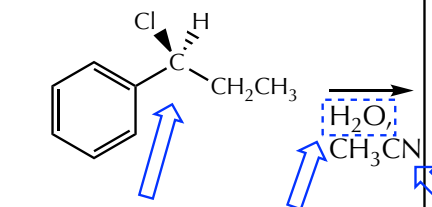


Elimination

In this molecule, the single elimination product from the one set of β-Hs does not have the possibility of forming (*E*) and (*Z*) diastereomers.

Now there are 3 β-Hs, and when any of the 3 of them is lost in an elimination reaction, the same product molecule forms because this outcome is not a double bond that can produce (*E*) and (*Z*) diastereomers. This little question requires three quite separate understandings:
(a) naming, because the structure is not provided
(b) that the overall reaction will not be any different, it's still the same E2
(c) a stereochemical analysis of the product

(g)



H_2O, CH_3CN

one of two stereoisomeric products containing oxygen

this is now key information, because the $S_N1/E1$ outcome is predicted to give all 4 possible products (see earlier, and below), but not all of them contain oxygen

+

one of two stereoisomeric products containing oxygen

the sp^3 C-LG is still!…

2˚with the possibility for resonance delocalization in a carbocation here

LB is…

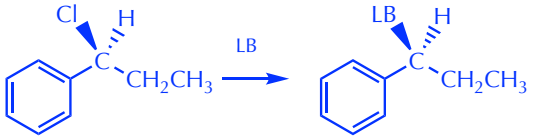
none of the Bronsted base categories

the solvent is polar

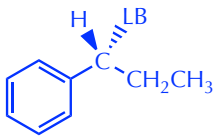
the carbocation is good

the solvent plays a role in the decision-making here; the Lewis base (water) is not in one of the Bronsted base categories for bimolecular reactions, so the question of unimolecular can be addressed; CH_3CN is a polar aprotic solvent

this combination predicts $S_N1/E1$; the $S_N1/E1$ outcome anticipates all possible products from substitution and elimination, unless experimental information is provided to limit the choice; here, the statements in the answer spaces provided such limits - a pair of "stereoisomeric products containing oxygen"; looking at the earlier generalization for all 4 possible substitution and elimination products, the elimination products do not depend on the identitiy of the Lewis base, while the substitution products integrate the Lewis base into their structures



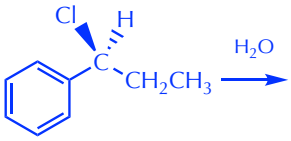
S_N with retention

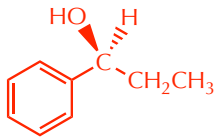


S_N with inversion

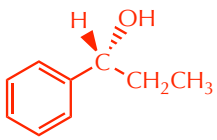
Elimination (Z)-isomer

Elimination (E)-isomer





S_N with retention



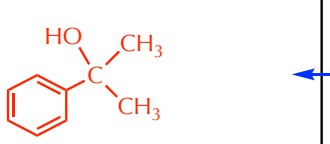
S_N with inversion

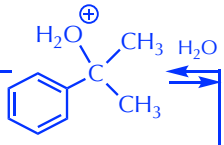
Although these two alcohols are consistent with all of the information in part (g), they are also linked explicitly to the information in part (h), so there is a chance to cross-check the validity of the answers: are they consistent with being able to apply this new information?

(h) When the two products that form in (g) are heated for an extended time in a strong aqueous acid solution, they both undergo an isomerization to give a single compound with the same molecular formula as the products in (g), and whose mechanism of formation proceeds through carbocation rearrangement. What is the structure of this isomerized product?

treatment with aqueous acid

isomerization via carbocation rearrangement





The text of the problem provides a number of key ideas, and the most important two are reiterated with the reaction arrow: "treatment with acid" and "isomerization via carbocation rearrangement" (the clear reading of the text is critically useful, because even isomerization is defined as giving a single compound "with the same molecular formula as the products in (g)." Sketching what is happening, off to the side, is going to be inevitably useful. To get a carbocation rearrangment you need to form a carbocation; to get a carbocation you need a good one (it is 2˚ with resonance stability) and you need the OH to become a leaving group (which it can in acid). Both of these alcohol products will give the same carbocation because the stereocenter is lost.