1st- and 2nd-order Substitution and Elimination Reactions Organizational Chart

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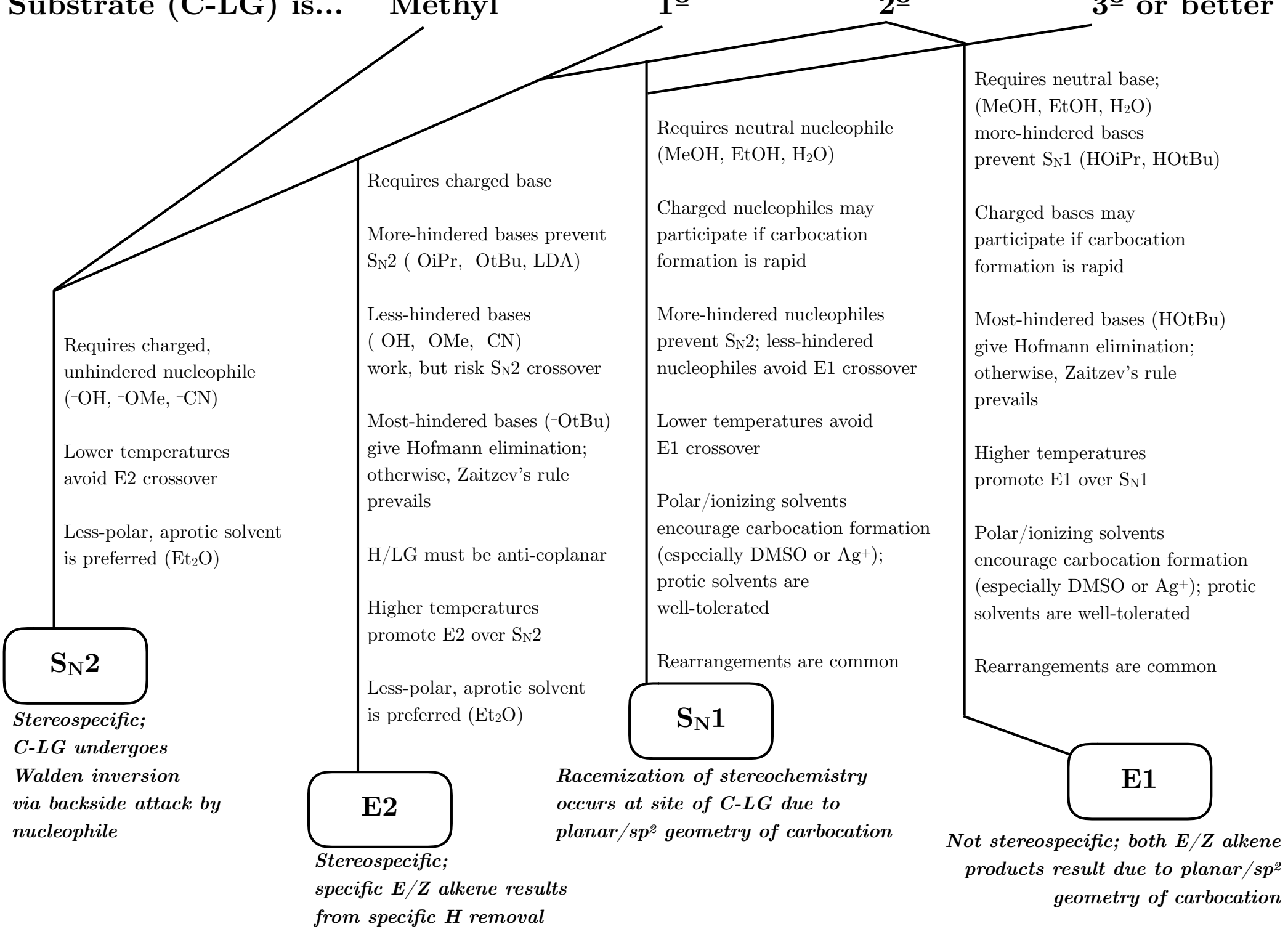
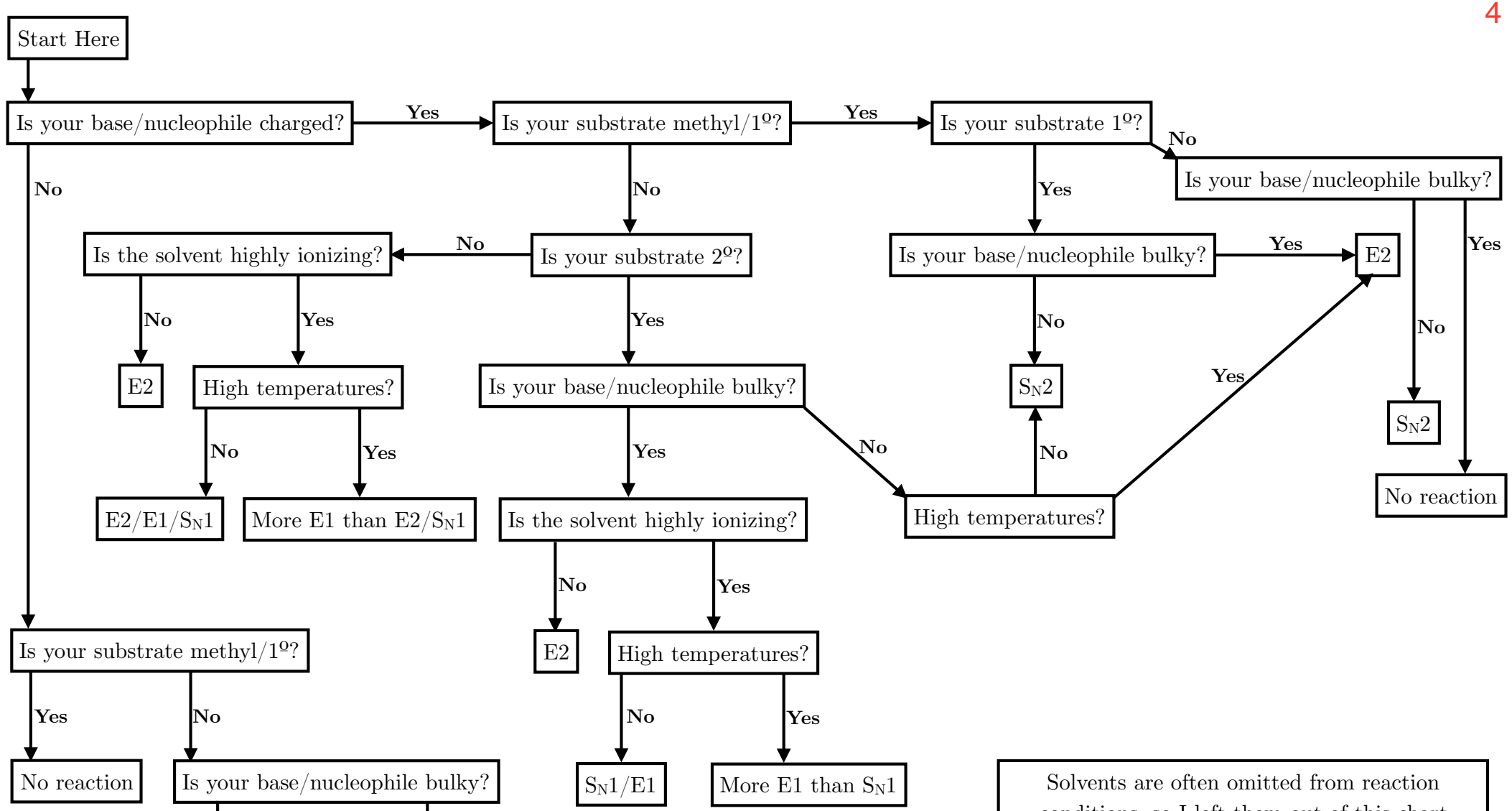
Notes

[1]For all mechanisms, a good leaving group is required; the leaving group must be a weaker base than the nucleophile or base being employed.
[2]A highly charged (−) nucleophile is required in order to generate sufficient electrostatic attraction with the δ^+ carbon bearing the leaving group.
[3]A partially charged (δ^-) nucleophile is sufficient to generate the requisite electrostatic attraction with the carbocation.
[4]A highly charged (−) base is required in order remove a hydrogen that is adjacent to the δ^+ carbon bearing the leaving group.
[5]A partially charged (δ^-) base is sufficient to remove a hydrogen that is adjacent to the carbocation.

Nucleophiles			**Leaving Groups**		**Bases**	
Strong	Moderate	Weak	Charged	Neutral	Zaitzev	Hofmann
$(CH_3CH_2)_3P$	Br^-	F^-	Cl^-	H_2O	HO^-	$(CH_3)_2HCO^-$
$(CH_3CH_2)_2NH$	NH_3	H_2O	Br^-	ROH	HS^-	$(CH_3)_3CO^-$
$(CH_3CH_2)_3N$	CH_3SCH_3	CH_3OH	I^-	NR_3	CH_3O^-	LDA
HS^-	Cl^-		$RSO_3{}^-$	PR_3	$CH_3CH_2O^-$	
HO^-			$RSO_4{}^-$	SR_2	H_2N^-	
I^-			$RPO_3{}^{2-}$		H^-	
$N{\equiv}C^-$						
CH_3O^-						
$N_3{}^-$						

Mechanism	Substrate (C-LG)	Kinetics	Stereochemistry	base/nucleophile	Leaving Group[1]	Solvent	Temperature	Rearrangements
S_N2	Methyl and 1°, but can be 2° if other conditions are ideal; accessibility of C-LG σ^* makes substitution of C-LG important	2nd order, rate = k[Nuc][RX]	Stereospecific; C-LG undergoes Walden inversion via backside attack by nucleophile	Nucleophile must be highly charged[2] and sterically unhindered; accessibility of C-LG σ^* makes bulkiness of nucleophile important	LG is displaced by the nucleophile directly	Less-polar solvents increase reactivity of nucleophile; must be aprotic; must be polar enough to dissolve a highly charged nucleophile	Lower temperatures avoid E2 crossover	No rearrangements can occur
S_N1	3°, allylic, and benzylic, but can be 2° if other conditions are ideal; stability of carbocation intermediate makes C-LG substitution important	1st order, rate = k[RX]	Racemization of stereochemistry occurs at site of LG due to planar/sp^2 geometry of carbocation	Nucleophile need not be highly charged[3] or sterically unhindered; smaller nucleophiles avoid E1 crossover; highly charged nucleophiles may participate if carbocation formation is rapid	LG leaves spontaneously due to stable carbocation formation and absence of strong nucleophile	Polar/ionizing solvent (especially DMSO or Ag^+) is required to stabilize charged intermediates; protic solvents are well-tolerated	Higher temperatures can promote carbocation formation but can lead to E1 crossover	Hydride, methyl, and ring shifts are common if carbocation and/or ring stability increases as a result of the rearrangement
E2	Any	2nd order, rate = k[Base][RX]	Stereospecific; β-H and LG must be anti-coplanar; specific E/Z alkene results from specific β-H removal; Zaitzev's rule applies to regiochemistry of alkene	Base must be highly charged[4]; sterically unhindered bases follow Zaitzev's rule; sterically hindered bases often give the Hofmann product	β-H and LG must be anti-coplanar; LG is displaced by population of C-LG σ^* by β-H bonding electrons upon their liberation by a strong base	Less-polar solvents increase reactivity of base; must be aprotic; must be polar enough to dissolve a highly charged base	Higher temperatures promote E2 over S_N2	No rearrangements can occur
E1	3°, allylic, and benzylic, but can be 2° if other conditions are ideal; stability of carbocation intermediate makes C-LG substitution important	1st order, rate = k[RX]	Not stereospecific; both E/Z alkene products result due to planar/sp^2 geometry of carbocation; Zaitzev's rule applies to regiochemistry of alkene	Base need not be highly charged[5] or sterically unhindered; bulkier bases favor E1 over S_N1; highly charged bases may participate if carbocation formation is rapid	LG leaves spontaneously due to stable carbocation formation and absence of strong base	Polar/ionizing solvent (especially DMSO or Ag^+) is required to stabilize charged intermediates; protic solvents are well-tolerated	Higher temperatures promote carbocation formation and favor E1 over S_N1	Hydride, methyl, and ring shifts are common if carbocation and/or ring stability increases as a result of the rearrangement


Substrate (C-LG) is...
Methyl
1º
2º
3º or better
Requires charged, unhindered nucleophile (⁻OH, ⁻OMe, ⁻CN)
Lower temperatures avoid E2 crossover
Less-polar, aprotic solvent is preferred (Et2O)
SN2
Stereospecific; C-LG undergoes Walden inversion via backside attack by nucleophile
Requires charged base
More-hindered bases prevent SN2 (⁻OiPr, ⁻OtBu, LDA)
Less-hindered bases (⁻OH, ⁻OMe, ⁻CN) work, but risk SN2 crossover
Most-hindered bases (⁻OtBu) give Hofmann elimination; otherwise, Zaitzev's rule prevails
H/LG must be anti-coplanar
Higher temperatures promote E2 over SN2
Less-polar, aprotic solvent is preferred (Et2O)
E2
Stereospecific; specific E/Z alkene results from specific H removal
Requires neutral nucleophile (MeOH, EtOH, H2O)
Charged nucleophiles may participate if carbocation formation is rapid
More-hindered nucleophiles prevent SN2; less-hindered nucleophiles avoid E1 crossover
Lower temperatures avoid E1 crossover
Polar/ionizing solvents encourage carbocation formation (especially DMSO or Ag+); protic solvents are well-tolerated
Rearrangements are common
SN1
Racemization of stereochemistry occurs at site of C-LG due to planar/sp² geometry of carbocation
Requires neutral base; (MeOH, EtOH, H2O) more-hindered bases prevent SN1 (HOiPr, HOtBu)
Charged bases may participate if carbocation formation is rapid
Most-hindered bases (HOtBu) give Hofmann elimination; otherwise, Zaitzev's rule prevails
Higher temperatures promote E1 over SN1
Polar/ionizing solvents encourage carbocation formation (especially DMSO or Ag+); protic solvents are well-tolerated
Rearrangements are common
E1
Not stereospecific; both E/Z alkene products result due to planar/sp² geometry of carbocation



Solvents are often omitted from reaction conditions, so I left them out of this chart with the exception of "highly ionizing" solvents (DMSO, Ag^+, etc.) because of their importance in promoting E1/S_N1 when these mechanisms would otherwise be unfavored. Uncharged bases/nucleophiles are usually polar protic solvents and promote E1/S_N1 while suppressing E2/S_N2. Less-polar aprotic solvents suppress E1/S_N1, and increase reactivity of charged species, promoting E2/S_N2.

Decision Logic

The most complicated scenario is with a 2° substrate, since all four mechanisms are accessible from there. The following steps are especially helpful for 2° substrates, but can be helpful even for methyl, 1°, and 3°(or better) substrates.

1. First, look at your base/nucleophile.
   - If it's **charged**, then E2/S_N2 are most likely.
   - If it's **uncharged**, then E1/S_N1 are most likely; you can rule out E2/S_N2.
   - Note that E1/S_N1 ***can*** occur with a **charged** base/nucleophile, ***if*** carbocation formation is rapid. So, if your base/nucleophile is charged...
2. Look at your solvent.
   - Highly polar and ionizing solvents like DMSO or H_2O/Ag^+ promote formation of carbocations. If you have a solvent like this, you can expect E1/S_N1 ***even if*** your base/nucleophile is charged. The solvent will accelerate carbocation formation, and will compete with the charged base/nucleophile long enough to inhibit the E2/S_N2 pathways until carbocation formation can occur.
   - If your solvent is polar and protic, then E1/S_N1 are most likely, regardless of whether or not your base/nucleophile is charged; you can rule out E2/S_N2. Charged bases/nucleophiles will undergo H^+ transfer with polar protic solvents, neutralizing their charge and slowing down the reaction enough to allow carbocation formation. Polar protic solvents also promote carbocation formation in the first place, further favoring E1/S_N1 pathways.
     - Uncharged bases/nucleophiles (like HOMe or HOEt) often act as the solvent for the reaction itself and thus should be considered as polar, protic solvents.
   - Less-polar, aprotic solvents like DMF, ethers, benzene, or hexanes, inhibit carbocation formation and increase reactivity of charged species, suppressing E1/S_N1 pathways and promoting E2/S_N2 pathways. There is a limit to this, however, as the solvent still needs to be polar enough to dissolve the charged base/nucleophile required for E2/S_N2.
3. If no solvent is given, simply assume that a **charged** base/nucleophile means that E2/S_N2 are most likely, and that an **uncharged** base/nucleophile means that E1/S_N1 are most likely (as in Step 1). You should now know whether your reaction will be first-order or second-order. Now, look at the steric hindrance (bulkiness) of your base/nucleophile.
   - If your base/nucleophile is sterically unhindered (small), then the nucleophilic pathways (S_N1/S_N2) are most likely. Unhindered species include, but are not limited to, $^-$OH, H_2O, $^-$OMe, HOMe, N_3^-, $^-NH_2$, NH_3, $^-C{\equiv}N$, and I^-.
   - If your base/nucleophile is sterically hindered (bulky), then the elimination pathways (E1/E2) are most likely, as well as S_N1 because S_N1 does not require an unhindered nucleophile like S_N2 does. Hindered species include, but are not limited to, $^-$OEt, HOEt, $^-$OiPr, HOiPr, $^-$OtBu, HOtBu, and LDA.
     - These species have a range of steric factors! In fact, the least-bulky bases in this list ($^-$OEt and HOEt) have a non-zero probability of acting as nucleophiles, especially when the substrate is less-highly substituted (and the C-LG σ^* is thus more accessible). For example, $^-$OEt, the least-bulky species here, acts as a **nucleophile** (in an S_N2 reaction) with 1-bromobutane (1°), but it acts as a **base** (in an E2 reaction) with 2-bromobutane (2°).
   - Note that the elimination pathways (E1/E2) ***can*** occur with sterically unhindered (small) bases. So, if your base/nucleophile is sterically unhindered (small) or if you're still undecided...
4. Look at temperature.
   - High temperatures promote ionization (E1/S_N1 over E2/S_N2) and elimination (E1/E2 over S_N1/S_N2), so this can be your final tiebreaker, if provided. For example, KOH ($^-$OH) at 100 °C provides excellent conditions for elimination, even though $^-$OH is not a big, bulky base.
   - If no temperature is given, then you are likely to have multiple, competing pathways and should expect a mixture of products to form.

Examples

1. 2-bromobutane with HOMe, no temperature given.
   - Substrate is 2°, so all pathways are available.
   - HOMe is uncharged (E1/S_N1 preferred) and protic (E1/S_N1 preferred), so we should expect first-order kinetics.
   - HOMe is unhindered, favoring S_N1 over E1; but we should expect some E1 products because elimination pathways ***can*** occur with sterically unhindered (small) bases.
   - Lowering temperatures could minimize E1 crossover, if desired.
2. 1-bromobutane with $^-$OMe, reflux (high temperature given).
   - Substrate is 1°, so we should expect second-order kinetics (E2/S_N2).
   - $^-$OMe is charged, so E2/S_N2 are again favored; even though E1/S_N1 can work with charged bases/nucleophiles under the right conditions, we can rule out first-order kinetics based on the 1° substrate.
   - $^-$OMe is unhindered, generally favoring S_N2 over E2; but we should expect some E2 products because elimination pathways ***can*** occur with sterically unhindered (small) bases.
   - High temperatures promote elimination, so we should expect significant E2 product. These conditions should thus give a mixture of E2 and S_N2 products. Reflux is likely to cause E2 to be the predominant pathway.
3. 2-bromo-2-methylbutane with HOiPr, no temperature given.
   - Substrate is 3°, so we should expect first-order kinetics (E1/S_N1).
   - HOiPr is uncharged (E1/S_N1 preferred) and protic (E1/S_N1 preferred), so we should expect first-order kinetics.
   - HOiPr is hindered, favoring E1 over S_N1; but we should expect some S_N1 products because S_N1 does not require an unhindered nucleophile.
   - This is likely a mixture of E1 and S_N1 pathways.
4. 3-bromo-2-methylbutane with H_2O/Ag^+, reflux (high temperature given).
   - Substrate is 2°, so all pathways are available.
   - H_2O is uncharged (E1/S_N1 preferred) and protic (E1/S_N1 preferred), with ionizing Ag^+, so we should expect first-order kinetics.
   - H_2O is unhindered, generally favoring S_N1 over E1; but we should expect some E1 products because elimination pathways ***can*** occur with sterically unhindered (small) bases.
   - High temperatures promote elimination, so we should expect significant E1 product. These conditions should thus give a mixture of E1 and S_N1 products. Reflux is likely to cause E1 to be the predominant pathway.
5. 2-bromobutane with $^-$OtBu, reflux (high temperature given).
   - Substrate is 2°, so all pathways are available.
   - $^-$OtBu is charged, so E2/S_N2 are favored; but, E1/S_N1 can work with charged bases/nucleophiles under the right conditions so we can't rule anything out yet.
   - $^-$OtBu is very bulky, so we can rule out S_N2.
   - High temperatures promote elimination, so we can expect mostly E1/E2. The absence of information regarding solvent means that we can't choose E1 or E2, but they often yield the same products. Since 2° substrates are on the poor side of the S_N1 range and $^-$OtBu is so sterically hindered (also on the poor side of the S_N1 range), we can largely rule out S_N1.