Compounds C and D were prepared to study how the tuberculosis bacterium operates during an infection (ACS Chem Biol, 2016, 11, 1810). Deprotonation of compound A gives its conjugate base, compound B, which can undergo a substitution reaction at two different sites because of delocalization of the negative charge (represented by resonance contributors B1 and B2).

(a) Provide resonance contributor B2, which is used to explain the formation of compound D.

(b) Provide the curved arrow mechanism for the formation of compound D from contributor B2.

(c) Complete the energy diagram for this reaction.

Notes:
(i) the pKa value of A is 7.25
(ii) the overall reactions to form C and D have the same ΔG° values; and
(iii) the second step is the rate-determining step.

Show:
(i) the energy level of compound B
(ii) the energy levels of compounds C and D
(iii) the energy curves for A to B, B to C, and B to D

(d) How would the experimental outcome have been different if this was a thermodynamically controlled reaction?
Compounds C and D were prepared to study how the tuberculosis bacterium operates during an infection (ACS Chem Biol, 2016, 11, 1810). Deprotonation of compound A gives its conjugate base, compound B, which can undergo a substitution reaction at two different sites because of delocalization of the negative charge (represented by resonance contributors B1 and B2).

(a) Provide resonance contributor B2, which is used to explain the formation of compound D.

(b) Provide the curved arrow mechanism for the formation of compound D from contributor B2.

(1) Compounds C and D are the two outcomes.

(2) Compound A is being deprotonated… but this is NOT an acid-base question - that topic is known!

This means you are expecting to see compound A behave as a Brønsted acid, losing a proton (H+) to a molecule that is behaving as a Brønsted base. At this point (Chapter 4), topics such as acid-base chemistry are now going to be assumed to be understood. After the first exam, if you are carrying misunderstandings about any of those earlier topics, you absolutely should be working to clear those up because (perhaps clearly) if you do not, you will be carrying that debt forward. This question is NOT an acid-base problem, but understanding acid-base chemistry is a pre-requisite knowledge that instructors are going to count on. In addition, some critical information or hints about the question are going to be expected to be able to be communicated using all of the earlier subject matter from the course.

(3) The conjugate base of compound A is compound B, of which two of its resonance contributors are used to explain the formation of products C and D… but this is NOT a resonance question - that topic is known!

Comparaably: the concept of drawing and understanding resonance contributors is an established idea in the course by this point, so being told explicitly about the pair of resonance contributors for compound B is intended to provide useful information to answer the question, which is how to associate a specific resonance contributor with the formation of compound D, from contributor B2.
Compounds C and D were prepared to study how the tuberculosis bacterium operates during an infection (ACS Chem Biol, 2016, 11, 1810). Deprotonation of compound A gives its conjugate base, compound B, which can undergo a substitution reaction at two different sites because of delocalization of the negative charge (represented by resonance contributors B1 and B2).

(a) Provide resonance contributor B2, which is used to explain the formation of compound D

(b) Provide the curved arrow mechanism for the formation of compound D from contributor B2.

(4) Compounds C and D are the two products of a substitution reaction that comes from the single compound B because a negative charge can be delocalized (and the understanding of that is further reinforced by repeating the information that delocalization means that compound B is going to be represented by two different resonance contributors whose negative charge will be located on different atoms).

Substitution reactions involving carbon atoms are a new topic. With these structural restrictions: an unhindered, that is, an uncrowded, sp\(^3\) carbon-halogen bond can be broken in a direct collision with many different examples of Lewis bases, where the Lewis basic group replaces - or substitutes for - the halogen atom.
Compounds C and D were prepared to study how the tuberculosis bacterium operates during an infection (ACS Chem Biol, 2016, 11, 1810). Deprotonation of compound A gives its conjugate base, compound B, which can undergo a substitution reaction at two different sites because of delocalization of the negative charge (represented by resonance contributors B1 and B2).

The fundamental information from Energy Diagrams:
• relative stabilities of different molecules [starting material(s), products(s), intermediate(s)]
• relative stabilities of different transition state structures that occur between these molecules
• predictive information about relative rates
• predictive information about product distributions when degree of reversibility is known

Notes:
(i) the pKa value of A is 7.25
(ii) the overall reactions to form C and D have the same \(-\Delta G^°\) values; and
(iii) the second step is the rate-determining step.

The reaction progress:
- \( \Delta G^° \) for that reaction
- \( E \) : the E of the transition state structure from \( Q \) to \( R \) or from \( R \) to \( Q \)
- \( Y \) : the E of the transition state structure from \( Q \) to \( S \) or from \( S \) to \( Q \)
- \( Q \) to \( R \) or \( Q \) to \( S \): the \(-\Delta G^°\) for that reaction
- \( X \) : the E of the transition state structure from \( Q \) to \( R \)
- \( R \) to \( X \) : the E of activation for \( Q \) to \( R \)
- \( Q \) to \( Y \) : the E of activation for \( Q \) to \( S \)
- \( S \) to \( Y \) : the E of activation for \( S \) to \( Q \)
- \( Q \) to \( S \) is faster than \( Q \) to \( R \)
- If all steps are reversible, then \( S > R > Q \) at equilibrium
- If forward steps are irreversible, then \( S > R \) at equilibrium
- because \( Q \) to \( Y \) is less than \( Q \) to \( X \)
- If \( Q \) to \( R \) is reversible and \( Q \) to \( R \) is irreversible, then only \( R \) is seen

Thus: compound A (pKa 7.25) + \( K_2CO_3 \) → compound B + KHCO_3 (pKa 10.2) is a favorable reaction. **Note** this difference in the E Diagrams when you are showing the entire reaction or the fact that the anion (B) is less stable than the uncharged molecule (A).
Compounds C and D were prepared to study how the tuberculosis bacterium operates during an infection (ACS Chem Biol, 2016, 11, 1810). Deprotonation of compound A gives its conjugate base, compound B, which can undergo a substitution reaction at two different sites because of delocalization of the negative charge (represented by resonance contributors B1 and B2).

Note (ii): “the overall reactions to form C and D have the same \(-\Delta G^\circ\) values” refers to the relationship between A and C, and A and D ... it also means, implicitly, that if C and D are equal in stability (same E level), they are formed unequally (61% D and 19% C), so the difference is a rate (activation E) difference. And indeed the question states explicitly that compound D forms faster than compound C; while both are higher than the A to B step.

(d) How would the experimental outcome have been different if this was a thermodynamically controlled reaction? As remarked in Blue Note (ii): “a reversible set of reactions would mean that C and D would be formed in equal amounts” (because they are equal in stability/energy. So: C and D would be formed in equal amounts.