In 1912, Carl Mannich, a Professor of Pharmaceutical Chemistry at the University of Göttingen, published a paper on a reaction that would come to bear his name: The Mannich Reaction (Archiv der Pharmazie, 1912, 250, 647). In the following problem, (a) provide the structure of the intermediate (A) that results from the curved arrows shown. Then, (b) using your intermediate, provide the arrows that are needed when intermediate A reacts with acetone enolate to give the observed products.

The curved-arrow notation is a shorthand representation used by organic chemists to indicate the changes in connectivity during chemical reactions. Because connectivity changes involve bond-making and bond-breaking, the notation is sometimes annoyingly referred to as “electron-pushing.”

The notation is a bookkeeping device. Following the principle of well-behaved atoms with highly predictable bonding patterns, the curved-arrow notation keeps track of which electrons have come from where as bonding changes take place.

The curved-arrow notation also tells a specific story about the timing of bond change events as a flow of electrons and thus a flow, or particular sequence, to the bonding changes. Conceptually, a person thinks about reading or laying down the arrows as a sequence in which the first arrow starts at the place where the electron (bonding change) flow begins, and ends with the final destination. Bonds change only one at a time, involving only one pair of electrons at the time, and with each arrow representing an electron pair.

The well-behaved nature of the atoms is critical: reactions will tend to maintain the useful generalizations, so changes will not usually violate those at all. There are plenty of times when formal charges will result, and these will also, too, be tracked by the changes represented by the curved arrows.

Sometimes the arrows are added to existing structures, to clarify the changes that have already been represented:

All of the information about a set of bonding changes is shown explicitly, so it is a matter of being able to read the organic chemistry.

Both oxygen atoms have closed shell electron configurations. The one on the right hand side is shown with 2 bonds and 2 nbe, so it has used one of the 3 nbe that are shown on the left to form the new C-O bond. In doing so, it goes from being an anion to being uncharged, so this oxygen anion on the left is the electron source for these changes.

Both chlorine atoms are also shown in their closed shell forms. The C-Cl bond on the left hand side has been broken, and the chlorine is in the form of the anionic chloride ion on the right. It has taken the shared pair from the C-Cl bond and now possesses those as its fourth nbe pair.
A. In 1912, Carl Mannich, a Professor of Pharmaceutical Chemistry at the University of Göttingen, published a paper on a reaction that would come to bear his name: The Mannich Reaction (Archiv der Pharmazie, 1912, 250, 647). In the following problem, (a) provide the structure of the intermediate (A) that results from the curved arrows shown. Then, (b) using your intermediate, provide the arrows that are needed when intermediate A reacts with acetone enolate to give the observed products.

![Diagram of the Mannich Reaction](image)

What is seen here, then, reading from left to right:
(a) the oxygen anion uses one of its nbe pairs to form a new C-O bond
(b) the C-Cl bond is broken and the electrons are used to make the new nbe pair of the chloride ion.

By convention, we think of the bonds breaking because new bonds are forming, and that the characteristics of these well-behaved atoms will be maintained: there will be closed shell configurations whenever possible.

Thus, the timing of these two bonding changes is critical to think about, as is the direction of the electron flow: where does the change begin and where does it end?

Atoms that go from being more negative to less negative are a good place to look for the electron source, while atoms that are getting more negative are likely to be the electron destination.

If the C-Cl bond breaks first, the chloride ion can form, but the carbon atom becomes open shell. Electrons cannot move towards the oxygen anion because it would exceed its closed shell. And the nbe pair from oxygen cannot form a new bond to the carbon atom without the C-Cl bond breaking, because then the carbon will exceed its octet.

Reading the equation from left to right, then, one of the nbe pairs from the oxygen atom is used to form a new C-O bond to the carbon where the chlorine atom sits, at the same time, the C-Cl bond breaks, sending that electron pair onto the chlorine atom, creating a new nbe pair on the released chloride ion. The sodium cation is a spectator ion, and remains uninvolved in any of the bonding changes. The sentences in this paragraph can be translated from words into the symbolism of the curved arrow notation.

“one of the nbe pairs from the oxygen atom is used to form a new C-O bond to the carbon where the chlorine atom sits”

“at the same time, the C-Cl bond breaks, sending that electron pair onto the chlorine atom, creating a new nbe pair on the released chloride ion”

“the first curved arrow begins here: and means “use this pair”

“the second curved arrow begins here: and means “use this pair”

“the first curved arrow starts at the O nbe and points to the C and means “use this pair to make a new C-O between these two atoms”

“the second curved arrow starts at the C-Cl bond and points to the Cl atom and means “break the bond and use this pair to make a new nbe at chlorine”

Although it is impossible to tell which arrow was drawn first, the mental process of this electron flow is absolutely the way these arrows are imagined in their use: a start-to-finish flow describing these changes.
A. In 1912, Carl Mannich, a Professor of Pharmaceutical Chemistry at the University of Göttingen, published a paper on a reaction that would come to bear his name: The Mannich Reaction (Archiv der Pharmazie, 1912, 250, 647). In the following problem, (a) provide the structure of the intermediate (A) that results from the curved arrows shown. Then, (b) using your intermediate, provide the arrows that are needed when intermediate A reacts with acetone enolate to give the observed products.

Start by identifying the electron flow and note the implied order of the arrows.

N nbe = starting point of electron flow

Only these two pairs are changing

The second part of the question asked to add the curved arrows needed when intermediate A combined with the acetone enolate to give the observed product.

The inventory of bonding changes is needed, and this begins with clearly identifying which atoms are from where; there are 6 changes associated with 3 pairs of electrons; the flow starts with the oxygen atom that starts off negative, and ends with the nitrogen, that goes from positive to uncharged.
A. In 1912, Carl Mannich, a Professor of Pharmaceutical Chemistry at the University of Göttingen, published a paper on a reaction that would come to bear his name: The Mannich Reaction *(Archiv der Pharmazie, 1912, 250, 647)*. In the following problem, (a) provide the structure of the intermediate (A) that results from the curved arrows shown. Then, (b) using your intermediate, provide the arrows that are needed when intermediate A reacts with acetone enolate to give the observed products.

You not only record bonding changes with the curved arrows, but also implicitly showing a flow of electrons: which electrons go where in forming new bonds and which ones go where when bonds break. This, the overall flow from oxygen (a) to nitrogen (g) needs to be captured, at least mentally, and it is certain that experienced learners would understand that there is a “first arrow” and a sequence in which the remaining arrows would be laid down, start from a and heading to g.

Last arrow ends here

First arrow starts here

Oxygen atom a forms a new bond at location b, while bond c has been broken and a new bond has formed between atoms d and e; one of the f bonds is broken, and a new lone pair is formed at nitrogen g.
And, as long as we are here, let’s go ahead to part B of the same question.

B. The biological preparation of nicotine, in some plants, uses a Mannich reaction as one of the key steps. Earlier on in the preparation of nicotine, however, the following reaction is observed. Provide the structures that result from the curved arrows, shown below. Include all necessary non-bonding electrons and formal charges. Provide the balanced equation.