

*Mechanisms  
in  
Organic  
Reactions*

*by* RICHARD A. JACKSON

# 23

## Mechanisms in Organic Reactions

RICHARD A. JACKSON

*University of Sussex*

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藏书章

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# Preface

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The wonderful complexity of organic chemistry involves thousands of different reactions which allow the synthesis and interconversions of millions of compounds, some of great complexity. The key to understanding this vital branch of chemistry is the concept of the reaction mechanism.

This book starts with a discussion of how covalent bonds break and form, and how these bond-breaking and bond-forming processes provide the basis of reaction mechanisms. The principles governing how to make sensible suggestions about possible mechanisms are set out, and the distinction is made between elementary reactions, which involve just one step, and stepwise reactions which have more than one step and involve the production of intermediates that react further.

Chapter 2 covers kinetics, which provides useful information about reaction mechanisms, and allows us to distinguish between possible mechanisms in many cases. Elementary reactions do not involve intermediates, but go through a transition state. Although this transition state cannot be isolated, it can be studied in various ways which provide insights into the reaction mechanism, and this forms the subject matter of Chapter 3. This is followed by three chapters on the most important intermediates in organic chemistry: anions, radicals and cations. A final chapter on molecular reactions concerns thermal and photochemical processes. The concepts of frontier orbitals and the aromatic transition state allow us to predict which reactions are “allowed” and which are “forbidden”, and provide insights into why most reactions of practical interest involve multi-step processes.

Where common names are used for organic compounds, the systematic name is given as well at the first mention. Common names are widely used in the chemical literature, in industry and commerce, and there is a great divergence in the use of systematic as opposed to non-systematic nomenclature in the English-speaking world.

I thank many colleagues for helpful comments and advice, particularly Mr Martyn Berry and Professor Alwyn Davies FRS who have read the entire manuscript and whose suggestions for changes have improved the text in numerous places. I would also like to thank my wife Pat for her support and forbearance over the past three years. Enjoy the book!

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*University of Sussex*

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# 1

## What Is a Mechanism?

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The chemical structure of most organic compounds is well established. Spectroscopic methods and X-ray crystallography show that individual atoms in a molecule are connected, usually by covalent bonds. Bond lengths are often known to within about  $\pm 1$  pm (0.01 Å) and bond angles to within  $\pm 1^\circ$ . Molecular models and graphics programs give a good picture of the overall shape of the molecule, including possible interactions between atoms that are not covalently bonded to each other. These structures correspond to energy minima.

Molecules can acquire extra energy by collisions, and this energy may cause distortions of bond lengths or angles by small amounts. However, the bond lengths and angles will tend to return to the equilibrium values.

However, if the distortions become too great, one or more covalent bonds may break, and new bonds may be formed, either within the molecule or with a new molecule with which the first has collided. A chemical reaction has occurred, and when equilibrium is reached, one or more new molecules will be produced, which may be stable or may undergo further reactions.

The energy required to break covalent bonds may be provided thermally by molecular collisions, which give a range of molecular energies, providing some molecules with enough energy to react. At higher temperatures, more molecules will have sufficient energy to react, so the reaction will be faster. Alternatively, the energy can be provided in other ways, especially by visible or UV light. Absorption of a photon by a molecule causes electronic excitation, and the excited state of the molecule may then undergo reactions which cannot be carried out thermally.

### Aims

This chapter describes the main features of organic reaction mechanisms and how “reasonable” mechanisms can be written. Having worked through this chapter you should be able to:

- Explain the importance of reaction mechanisms in organic chemistry
- Understand the difference between elementary and stepwise reactions, and the role played by transition states and intermediates
- Know the main types of bond-breaking and bond-making processes
- Identify the bonds made and broken in a reaction, given the starting materials and products, thereby allowing a number of possible reaction mechanisms to be written
- Cut down the number of possible mechanisms by using the concepts of energy and molecularity requirements

## 1.1 Elementary and Stepwise Reactions

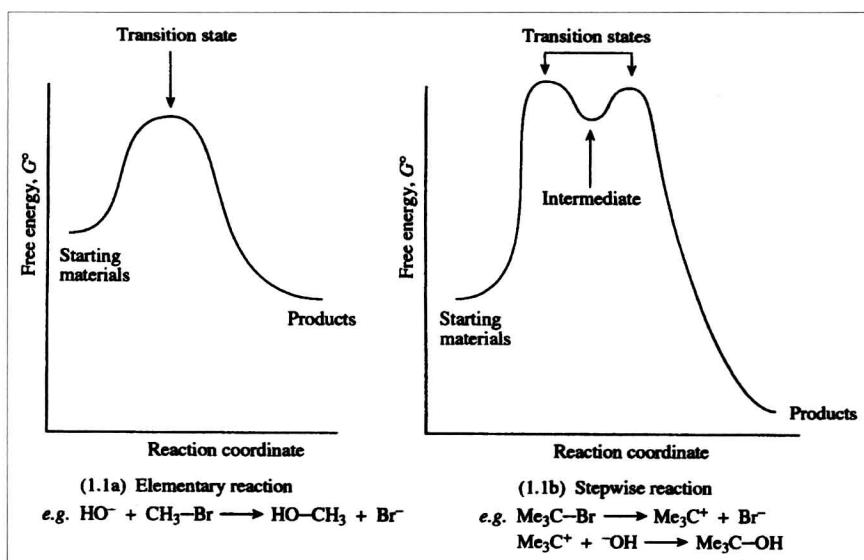
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Reactions are of two types. In elementary reactions the reacting molecule or molecules are transformed into products directly, without the formation of intermediates. In a stepwise reaction, one or more intermediate species are produced, which react further to give the products. A stepwise reaction can be split up into two or more elementary reactions.

As an elementary reaction proceeds, the Gibbs free energy increases up to a maximum value and then goes down to a value corresponding to that of the products. The position of highest energy is called the transition state, and is a key feature of the reaction; most of the experimental information about chemical reactions relates to the transition state and will be discussed in the next two chapters.

In a stepwise reaction, at least one of the products of the first elementary reaction reacts further in a second elementary reaction. This may be followed by further elementary reactions until the reaction is complete. Any molecules produced in the course of a stepwise reaction which react further and are not present at the end of the reaction are known as **intermediates**. Intermediates are discussed in more detail in Chapters 4, 5 and 6.

Figure 1.1 shows free energy diagrams for an elementary reaction (1.1a) and for a stepwise reaction with two steps (1.1b).



**Figure 1.1** Free energy diagrams for elementary and stepwise reactions

An example of an elementary reaction (1.1a) is the  $\text{S}_{\text{N}}2$  displacement of a bromide ion from bromomethane by the hydroxide anion. The reaction is thermodynamically favourable (negative  $\Delta G^\circ$ ) and takes place when a hydroxide ion collides with a bromomethane molecule. A bond starts to form between the oxygen atom and the carbon atom at the same time as the carbon-bromine bond breaks. Because of electron repulsion, in the early stages of the reaction the energy released by the formation of the new bond is not quite as much as the energy required to break the C–Br bond, so the free energy increases and eventually reaches a maximum at the transition state, before decreasing to the value appropriate to the products. No intermediate is involved; the reaction proceeds smoothly from reagents through the transition state directly to products.

In contrast, the hydrolysis of *tert*-butyl bromide (2-bromo-2-methylpropane) occurs in a stepwise manner (reaction 1.1b). In the first slow step, the C–Br bond breaks, with the bromine atom taking both electrons from the bond and leaving as a negatively charged bromide ion. The remainder of the molecule is the positively charged *tert*-butyl cation (2-methylprop-2-yl cation). This is a highly reactive intermediate, which reacts rapidly with the hydroxide ion to form the corresponding alcohol.

**Box 1.1 Elementary and Stepwise Reactions**

In an elementary reaction, reacting molecules are transformed into products without going through intermediates. A stepwise reaction involves consecutive elementary reactions where the intermediate(s) produced in the first elementary reaction react further in subsequent elementary reactions.

Mechanisms cannot be established just by looking at the structures of reactants and products.

These two examples raise an important point about mechanisms. The two reactions are similar from the point of view of reagents and products, yet are known to have different mechanisms. Thus we cannot determine mechanisms merely by knowing the starting materials and products; we need further information. The remainder of this chapter is devoted to writing sensible possible mechanisms for a new reaction, and the remainder of the book concerns the methods that we can use to distinguish between the various mechanistic possibilities.

## 1.2 Bond Making and Bond Breaking

Inspection of the structure of the reagents and products tells us which covalent bonds have been broken and formed during the reaction.

### 1.2.1 Bond Breaking

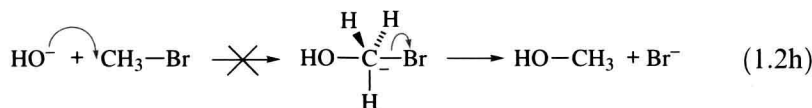
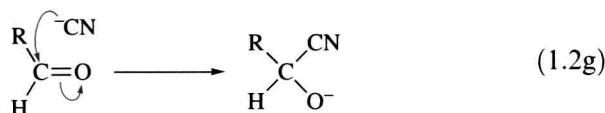
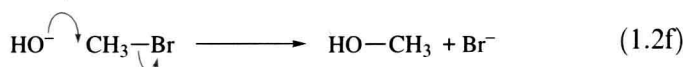
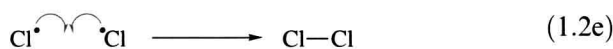
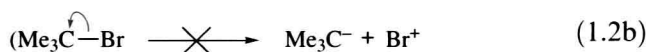
Covalent bonds, which involve two electrons, can be broken in two ways, homolytically (homo = same), when one electron is retained by each fragment, or heterolytically (hetero = different), when both electrons go to one of the fragments. Heterolysis is more likely if the two atoms in the bond have different electronegativities, and in polar solvents which stabilize charges. Electronegativity is a measure of the power of an atom or a group of atoms to attract electrons from other parts of the same molecule: fluorine is the most electronegative element; cesium is the most electropositive. A covalent bond between two different elements is polarized in the direction  $\delta^+X-Y\delta^-$ , where Y is the more electronegative element. In a heterolysis, the bond will almost always break in the direction which will leave both bonding electrons on the more electronegative atom. If the original molecule has no net charge, this will give an anion centred on the more electronegative element and the cation centred on the less electronegative element. The electronegativities of elements commonly found in organic compounds are listed in Table 1.1.


**Table 1.1** Electronegativities of elements commonly found in organic compounds<sup>a</sup>


H						
2.1						
Li	Be	B	C	N	O	F
1.0	1.5	2.0	2.6	3.0	3.4	4.0
Na	Mg	Al	Si	P	S	Cl
0.9	1.3	1.6	1.9	2.2	2.6	3.2
K						Br
0.8						3.0
						I
						2.7

<sup>a</sup>Low numbers = electropositive; high numbers = electronegative

The first stage of the  $S_N1$  reaction in reaction (1.1b) is a heterolysis involving a neutral molecule dissociating into a cation and an anion. Heterolysis will take place exclusively in the direction indicated in reaction (1.2a), with no contribution from (1.2b). For the heterolysis shown in (1.2a), the electrons originate in the covalent bond; both move to the bromine atom during the reaction.



We show the movement of an **electron pair** in a reaction by a **curved arrow**.  The tail of the arrow shows the origin of the electrons that move, the head shows where they end up; thus the arrow gives a good representation of the movement of an electron pair during a reaction.

**Half-headed curved arrows (fish-hooks)**, , may be used to show the movement of **single electrons** during a free radical reaction. Because they are more awkward to draw and give a cluttered look to the reaction scheme, curved arrows are less commonly used in homolytic than in heterolytic processes.

Homolysis is more likely for weak covalent bonds and for bonds containing atoms with similar electronegativities. Heating di-*tert*-butyl

peroxide affords an example of homolysis (equation 1.2c). The central O–O bond breaks homolytically to give two *tert*-butoxyl radicals. Since one electron from the two shared electrons in the covalent bond goes to each atom, no charge is created during an homolysis.

### 1.2.2 Bond Formation

This is the reverse of bond breaking. The electrons involved in the new bond may both come from one of the reagents; this is the reverse of heterolysis. An example is the second step of reaction (1.1b), redrawn in (1.2d) to show the movement of an electron pair from an unshared pair on the oxygen atom (arrow-tail) to a position between the oxygen and the carbon atom where the covalent bond will form (arrow-head). Since an unshared electron pair becomes shared during bond formation, the oxygen effectively loses one electron and the formal negative charge on the oxygen atom is reduced from  $-1$  to zero. Likewise, the positively charged carbon atom acquires a half-share of two electrons and its formal charge changes from  $+1$  to zero.

If one electron comes from each of the atoms forming the new bond (the reverse of homolysis), there will be no change in formal charge (half of two shared electrons is equivalent to one attached to an individual atom). The combination of two chlorine atoms to form a chlorine molecule is shown in reaction (1.2e); the curved half-arrows show the movement of the electron from the chlorine atom (tail) to the position where the bond will be (head).

#### Box 1.2 Formal Charge

A carbon atom is electrically neutral if it has four electrons in its valence shell. It is also formally neutral in methane: though surrounded by eight electrons, these are all shared, and are equally involved in balancing the charge on the carbon and the four hydrogen atoms. For each electron pair, one can be formally considered as neutralizing the positive charge on a hydrogen atom; the other will contribute to neutralizing the charge on the carbon atom. Thus the carbon atom will formally have  $8/2 = 4$  electrons in its valence shell and will be electrically neutral. In a carbanion such as  $\text{CH}_3^-$  (see below) there are six shared electrons (counting  $6/2 = 3$ ) and two unshared electrons (belonging exclusively to the carbon atom). This gives five electrons, one more than the number needed for a neutral carbon atom, so the carbon atom has a formal negative charge. Formal charges for some carbon, nitrogen and oxygen species are shown below.

	$\cdot\ddot{\text{C}}\cdot$	$\begin{array}{c} \text{H} \\   \\ \text{H}-\text{C}-\text{H} \\   \\ \text{H} \end{array}$	$\begin{array}{c} \text{H} \\   \\ \text{H}-\text{C}^{\cdot}-\text{H} \end{array}$	$\left[ \begin{array}{c} \text{H} \\   \\ \text{H}-\text{C}-\text{H} \end{array} \right]^+$	$\left[ \begin{array}{c} \text{H} \\   \\ \text{H}-\ddot{\text{C}}-\text{H} \\   \\ \text{H} \end{array} \right]^-$
Valence shell electrons	4	$8/2 = 4$	$(6/2) + 1 = 4$	$6/2 = 3$	$(6/2) + 2 = 5$
Charge	neutral	neutral	neutral	+1	-1
	$\cdot\ddot{\text{N}}\cdot$	$\begin{array}{c} \text{H} \\   \\ \text{H}-\ddot{\text{N}}-\text{H} \\   \\ \text{H} \end{array}$	$\begin{array}{c} \text{H} \\   \\ \text{H}-\ddot{\text{N}}^{\cdot}-\text{H} \end{array}$	$\left[ \begin{array}{c} \text{H} \\   \\ \text{H}-\ddot{\text{N}}-\text{H} \end{array} \right]^+$	$\left[ \begin{array}{c} \text{H} \\   \\ \text{H}-\ddot{\text{N}}^{\cdot}-\text{H} \\   \\ \text{H} \end{array} \right]^-$
Valence shell electrons	5	$(6/2) + 2 = 5$	$(4/2) + 3 = 5$	$(4/2) + 2 = 4$	$(4/2) + 4 = 6$
Charge	neutral	neutral	neutral	+1	-1
	$\cdot\ddot{\text{O}}\cdot$	$\begin{array}{c} \text{H} \\   \\ \text{H}-\ddot{\text{O}}-\text{H} \\   \\ \text{H} \end{array}$	$\begin{array}{c} \text{H} \\   \\ \text{H}-\ddot{\text{O}}^{\cdot}-\text{H} \end{array}$	$\left[ \begin{array}{c} \text{H} \\   \\ \text{H}-\ddot{\text{O}}-\text{H} \end{array} \right]^+$	$\left[ \begin{array}{c} \text{H} \\   \\ \text{H}-\ddot{\text{O}}^{\cdot}-\text{H} \\   \\ \text{H} \end{array} \right]^-$
Valence shell electrons	6	$(4/2) + 4 = 6$	$(2/2) + 5 = 6$	$(2/2) + 4 = 5$	$(2/2) + 6 = 7$
Charge	neutral	neutral	neutral	+1	-1

These formal charges at specified atoms do not depend on the type of atom at the other end of the bond, so for example the oxygen atom in the methoxide ion  $:\ddot{\text{O}}-\text{CH}_3$  will have the same formal negative charge as the oxygen atom in  $^-\text{OH}$ .

### 1.2.3 Timing of Electron Movements

The hydrolysis of halogenoalkanes involves the breaking of a carbon–halogen bond and the formation of a carbon–oxygen bond. If the reaction is heterolytic, there are three mechanistic possibilities. The first is that bond breakage takes place first, followed by bond formation, as in reaction (1.1b). The difficulty with processes of this type is that they often have a high activation energy.

Alternatively, both bond-breaking and -making take place at the same time. For example, in reaction (1.1a), as the carbon–halogen bond breaks, the new carbon–oxygen bond is forming. The energy required for bond breakage is partially provided by the energy given out as the new bond forms. Processes of this type, with simultaneous bond-breaking and -making, are termed **concerted**. We show the movement of electrons as two (or more) curved arrows, as in reaction (1.2f). Since electrons are flowing both towards and away from the central carbon atom, little or no charge is built up there during the reaction. Concerted reactions may also involve attack by a reagent at an unsaturated centre. Here the bond

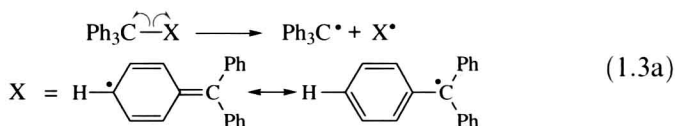
Concerted processes usually involve less activation energy than stepwise processes where a bond has to be broken before a new bond is formed. Almost all biological reactions, which are constrained by the need to take place at relatively low temperatures, are concerted.

broken is the double bond, leaving a charge or a radical centre at the other end of the bond. An example is shown in reaction (1.2g). Note the movement of an electron pair from the  $\pi$  bond to the oxygen atom.

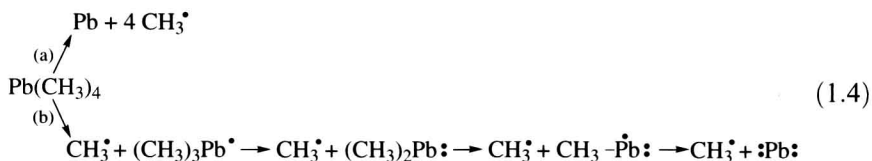
The third possibility, that bond formation precedes bond breakage, is not feasible at saturated carbon centres. Atoms of first-period elements cannot expand their octet, and carbon atoms cannot form more than four covalent bonds, so that mechanisms such as that shown in reaction (1.2h) can be ruled out.

Free radical reactions show the same timing possibilities as heterolytic processes. Reactions (1.3a–c) illustrate a non-concerted and two types of concerted reaction. More detailed consideration of homolytic processes will be given in Chapter 6.

<sup>Ph</sup>h = phenyl = C<sub>6</sub>H<sub>5</sub>

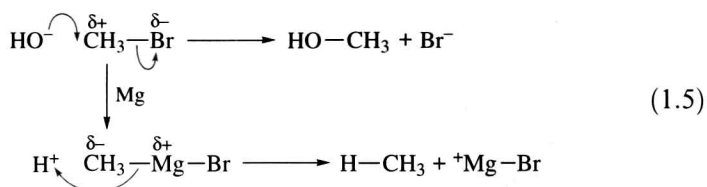


When postulating mechanisms, concerted possibilities should be considered first, then processes that require one bond to be broken at the start of the reaction process. Steps in which more than one bond is broken before any new bonds are formed can normally be ruled out as requiring too much energy. Thus the homolysis of tetramethyllead to give lead and four methyl radicals is more likely to proceed by the sequential homolysis of the four carbon–lead bonds (reaction 1.4b) rather than by simultaneous rupture of all four bonds (reaction 1.4a).



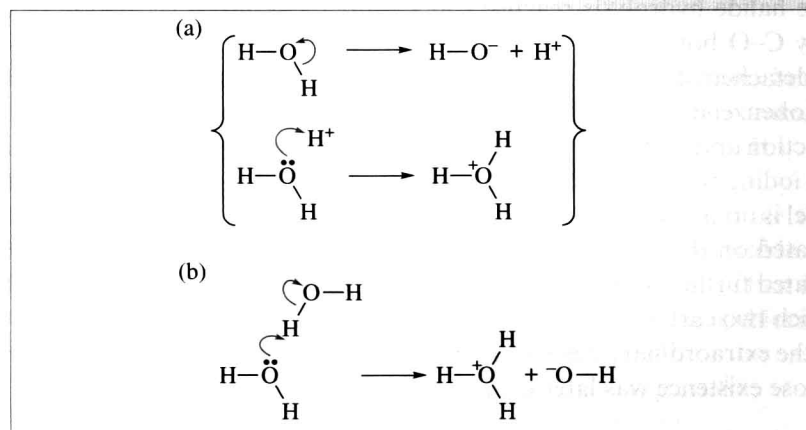
For heterolytic reactions, consideration of polarity is important in predicting possible reaction paths: positive reagents tend to react with the negatively polarized atom of a covalent bond and *vice versa*. Thus bromomethane, with  $\delta^+\text{C}$ , reacts with  $^-\text{OH}$  to give methanol, but not with a proton to give methane (reaction 1.5). If the bromomethane is allowed to react with magnesium to form methylmagnesium bromide, the polarity is reversed, giving  $\delta^-\text{C}$ , which reacts with acids to give methane

and not with bases to give methanol. Polar reactions are considered in more detail in Chapters 4 and 5.



### Worked Problem 1.1

**Q** In liquid water, small concentrations of hydroxonium ions,  $\text{H}_3\text{O}^+$ , and hydroxide ions,  $\text{OH}^-$ , are present. Two possible mechanisms for this dissociation are shown below. Which process is the more likely?



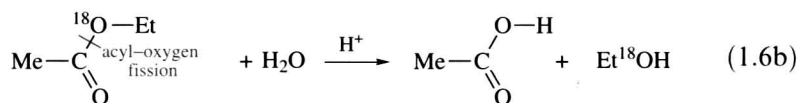
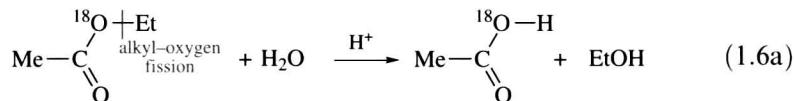
**A** In (a), the first step involves breakage of a strong covalent bond, which will require a large amount of energy and an activation energy of at least this amount. In (b), a bond is formed simultaneously with bond breakage, so the reaction is much less endothermic and the activation energy is likely to be considerably lower.

### 1.2.4 Labelling

It may often be obvious which bonds are broken and formed in a reaction. However, in some cases it is not so obvious. In the acid-catalysed hydrolysis of esters (reaction 1.6), it is not obvious whether the alkyl-oxygen bond is broken (1.6a) or the acyl-oxygen bond (1.6b). This question can be resolved by use of an  $^{18}\text{O}$  isotopic label in the ester.

Route (1.6a) predicts that the  $^{18}\text{O}$  label will end up in the carboxylic acid, whereas route (1.6b) predicts labelling of the alcohol. By mass spectrometry, it is established that the  $^{18}\text{O}$  label ends up in the alcohol, thus showing that acyl-oxygen fission takes place (reaction 1.6b). Note that neither (1.6a) nor (1.6b) represents complete mechanisms: the timing of the bond breaking and bond formation is not established, nor is the role of the acid catalyst. However, all the possibilities represented by (1.6a) are eliminated, simplifying the mechanistic search.

Et = ethyl =  $\text{C}_2\text{H}_5$   
Me = methyl =  $\text{CH}_3$



Sometimes a reaction is more complicated than appears at first sight. The halide hydrolysis reactions in Figure 1.1 result in formation of the new C-O bond at the same carbon atom from which the bromide ion is detached. However, in the apparently analogous reaction in which iodobenzene reacts with the amide ion to give aniline (phenylamine), the reaction does not go by route (1.7a). Carbon labelling of the atom to which the iodine atom is attached shows that in the aniline product about half the label is on the carbon attached to the  $\text{NH}_2$  group, whereas the other half is located on the adjacent carbon atoms. Significantly, none of the label is located further away. This shows that an intermediate must be formed in which two carbon atoms have become equivalent, leading to the proposal of the extraordinary benzyne intermediate in route (1.7b), an intermediate whose existence was later demonstrated by trapping experiments.

