

# **Guide to Organic Stereochemistry**

from methane to macromolecules

有机立体化学入门

**S. R. Buxton & S. M. Roberts**

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# Guide to Organic Stereochemistry

**Sheila R. Buxton**

**and**

**Stanley M. Roberts**

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# Preface

Stereochemistry is one of the most important scientific concepts and also one of the hardest areas of chemistry to grasp. Its importance is manifest not only in chemistry but also in many other of the life sciences. To acquire a good understanding of stereochemistry and its effects, one must be able to think and visualize in three dimensions and become familiar with the extensive and often confusing terminology.

*Guide to Organic Stereochemistry* is not intended to be a comprehensive text. However, we envisaged a book that would be a step-by-step guide for the beginner and also one that would provide some insight into how a knowledge of stereochemistry is used in planning synthetic strategy or rationalizing the outcome of some reactions.

The early chapters were constructed with the first-year undergraduate chemistry student in mind, and also possibly those engaged in the biochemical or medical disciplines, where an awareness of stereochemistry and its effects is necessary, but not the complexities. These chapters cover the identification and assignment of various chiral features of organic molecules, and, while assuming a level of understanding of general chemistry, do not require any prior knowledge of stereochemistry.

The middle chapters are orientated more to the advanced undergraduate chemistry student, where an understanding of the predictive capabilities of stereochemical models, Cram's rule for example, and of the more advanced stereochemical terminology, such as topicity or stereoselectivity, becomes more important.

After much thought, we decided also to discuss towards the end some of the more difficult and thought-provoking stereochemical topics of asymmetric synthesis, with the final chapter illustrating how these techniques have been used to make two complex, chiral, natural products. As this was thought likely to be of interest largely to early postgraduate chemists, the text is written more in the usual research style.

As mentioned above, *Guide to Organic Stereochemistry* is not intended to be comprehensive; for those interested enough to wish to read further around this subject, we strongly recommend Eliel and Wilen's excellent text *Stereochemistry of Organic Compounds*.

Whatever the level of the reader of this book, there is one thing that we do advocate unreservedly, and that is, to read the text in conjunction with a

molecular modelling kit. Building representations of chiral molecules and comparing their various stereoisomeric forms is invaluable for a proper understanding of stereochemical concepts. It is often astonishing how something that is almost impossible to visualize in two dimensions on a sheet of paper becomes crystal clear when constructed into a three-dimensional model. During the writing of this book, we tried a number of different modelling kits, and the best ones in our opinion, in terms of cost and effectiveness, were the Darling models. However, even a basic inexpensive kit, such as the Orbit set, can be an enormous aid to comprehension.

Finally, there are a number of questions set in each chapter, which sometimes present points not otherwise exemplified in the chapter. They are intended to make the reader extrapolate from what has been learned from the text, and thus it is important that the problems be attempted.

It is appropriate here to acknowledge the many people who have offered us assistance and encouragement during the preparation of the text. For practical work (preparation of Mosher's esters, determining  $[\alpha]_D$  values and running NMR spectra) we thank Dr Vladimir Sik and Dr Richard Hufton and for critical reading of all or parts of the manuscript we are indebted to Dr Gordon Read, Dr Brian Ridge, Dr Elena Lasterra, Dr Alex Drake, Professor Mark Baird, Professor Don Bethell, Professor Wes Borden, Miss Kathryn Wright, Miss Alison Murphy, Mr Stephen Hermitage, Dr Nazir Bashir, Mr Thierry Guyot, Mr Pierre Kary, Mr David Varley and Mr Daniel Watson. Special thanks go to Professor Milos Hudlicky for many ideas and suggestions.

The photographs of crystal structures of selected proteins, featured on the front cover and on pages 173 and 174, were kindly provided by Dr Jenny Littlechild (Exeter University). The Institut Pasteur (Paris) provided the photographs of Louis Pasteur's notebook and models (front cover and page 100).

Professor Ray Abraham and Drs Andrew Carnell, Rick Cosstick, Ian O'Neil and Dick Storr assisted at the proof-reading stage and Miss May-Britt Nielsen, Mr Pierre Kary, Mr Stephen Hermitage and Mr Daniel Watson helped in the compilation of the index.

*Sheila R. Buxton  
Stanley M. Roberts  
1996*

# Foreword

We live in a three-dimensional world at every level from the molecular to the macroscopic. Nowhere is the third dimension more important than in the field of organic chemistry. The study of chemistry in three dimensions is called 'stereochemistry'. In 1860, Pasteur described his famous resolution of tartaric acid, thereby giving birth to the field. A major step forward was taken by van't Hoff and Le Bel who recognised that a carbon with four bonds was tetrahedral, thereby providing the foundation for the modern concepts of stereoisomerism. But it was not until later that the study of the conformations of organic molecules brought the field of organic chemistry off the flat, two dimensional pages of chemistry journals forever and added the fourth dimension of time to the three geometric dimensions.

In the 1990s, stereochemistry pervades every aspect of the field of organic chemistry, and it is simply not possible to study any aspect of this field without a solid knowledge of stereochemistry. But the principles and players in stereochemistry — configuration, conformation, enantiomerism, diastereoisomerism, asymmetric synthesis, chiral auxiliaries, and so on — are not at all self-evident to aspiring organic chemists. Indeed, stereochemistry and its associated chemical consequences must surely be one of the reasons why many otherwise very bright students find introductory courses in organic chemistry so difficult. As the field continues to grow, the gap between the basic principles taught in introductory courses and the sophisticated applications of these principles in advanced books, review articles and original research papers grows ever wider.

The book by Roberts and Buxton steps boldly into this gap by providing a bridge for students. It helps them cross from the introductory level over to the real world with illustrations showing the principles and applications of stereochemistry. Sixteen easy-to-read chapters take students all the way from the shape of methane through the sophisticated and beautiful world of enzymes, to the elegant field of asymmetric synthesis. The book conveys the importance and the excitement of the field of stereochemistry along with its principles. Students taking the time and effort to cross the bridge with the aid of Roberts and Buxton's book will marvel at what they begin to see on the other side as the field of stereochemistry begins to unfold for them.

Dennis P. Curran  
*Distinguished Service Professor of Chemistry*  
*University of Pittsburgh*  
July 1996

# Contents

*Preface* vii

*Foreword* ix

## **1 SHAPES OF SIMPLE MOLECULES 1**

- 1.1 Methane 1
- 1.2 Hybridization 2
- 1.3 Ethene and ethyne 2
- 1.4 Molecules containing elements other than carbon 5
- 1.5 Conformation 8
  - 1.5.1 Ethane 8
  - 1.5.2 Butane 9
  - 1.5.3 Unsymmetrically substituted alkanes 10
- 1.6 Conformations of cyclic molecules 11
  - 1.6.1 Cyclohexane 11
  - 1.6.2 Substituents on cyclohexane 13
  - 1.6.3 Cyclohexene and cyclohexanone 14
  - 1.6.4 Smaller rings 15
  - 1.6.5 Cyclopropane 16
  - 1.6.6 Polycyclic compounds 16
  - 1.6.7 Heterocyclic ring systems 17

Answers to questions 18

## **2 CHIRALITY IN MOLECULES CONTAINING ASYMMETRICALLY SUBSTITUTED TETRAHEDRAL CENTRES 20**

- 2.1 Chiral molecules with one stereogenic centre: enantiomers 21
  - 2.1.1 Optical activity 21
  - 2.1.2 Specific rotation 22
  - 2.1.3 Racemates 22
- 2.2 Chiral molecules with two stereogenic centres:  
diastereoisomers 23
  - 2.2.1 Reaction of enantiomers with chiral reagents 23
  - 2.2.2 The Cahn-Ingold-Prelog (CIP) sequence rule 25
- 2.3 Pseudoasymmetric centres and *meso*-compounds 28
  - 2.3.1 *meso*-Compounds 28
  - 2.3.2 Pseudoasymmetric centres 29



2.4	Prochiral centres	30
2.4.1	<i>pro-R</i> , <i>pro-S</i>	31
2.5	Axes of symmetry	32
2.6	Representing three-dimensional molecules in two dimensions	33
	Answers to questions	34
<b>3</b>	<b>NOMENCLATURE AND STEREOCHEMISTRY OF AMINO ACIDS AND SOME SIMPLE CARBOHYDRATES</b>	<b>36</b>
3.1	Stereochemical descriptors: D and L notation, and Fischer projections	36
3.2	Nomenclature and stereochemistry of C <sub>4</sub> carbohydrates and tartaric acid	38
3.3	C <sub>5</sub> and C <sub>6</sub> carbohydrates	39
	Answers to questions	46
<b>4</b>	<b>CHIRALITY IN SYSTEMS LACKING A STEREOGENIC CARBON ATOM</b>	<b>48</b>
4.1	Point chirality	48
4.1.1	Tertiary amines and phosphines	48
4.1.2	Phosphine oxides, amine oxides and sulfoxides	49
4.2	Axial chirality	50
4.2.1	Allenes	50
4.2.2	Biphenyls and binaphthyls	52
4.3	Helical structures	54
4.3.1	Polynucleotides	55
4.3.2	Poly(amino acids)	55
4.3.3	Biaryls and allenes	58
	Answers to questions	59
<b>5</b>	<b>STEREISOMERISM ABOUT BONDS OF RESTRICTED ROTATION: CIS-TRANS ISOMERISM</b>	<b>60</b>
5.1	Stereochemistry in cyclic systems	60
5.1.1	<i>cis-trans</i> Nomenclature	60
5.1.2	<i>exo-endo</i> , <i>syn-anti</i> Nomenclature	64
5.2	Stereoisomerism about double bonds	65
5.2.1	<i>E</i> , <i>Z</i> -nomenclature	65
5.2.2	Structures of partial bond order	67
5.3	<i>cis-trans</i> Isomerism, enantiomerism and diastereoisomerism	69
5.4	<i>cis-trans</i> Isomerism in nitrogen-containing compounds	70
	Answers to questions	71
<b>6</b>	<b>METHODS FOR ESTIMATING RATIOS OF STEREOISOMERS IN A MIXTURE AND THE SEPARATION AND IDENTIFICATION OF THE INDIVIDUAL COMPONENTS</b>	<b>72</b>
6.1	Estimating ratios of stereoisomers	72
6.1.1	NMR spectroscopy	72
6.1.2	NMR and isomer ratios	75
6.2	Separating isomers	79

6.3	Identifying individual stereoisomers	84
6.3.1	NMR spectroscopy	84
6.3.2	Optical activity	86
6.3.3	X-ray crystallography	87
6.3.4	The Cotton effect	89
	Answers to questions	93
7	SOME TRANSFORMATIONS AT OR NEAR A STEREOGENIC CENTRE: RACEMIZATION AND RESOLUTION	95
7.1	Racemization	95
7.2	Resolution of a racemate	98
	Answers to questions	104
8	SOME SIMPLE REACTIONS OF CARBONYL COMPOUNDS	106
8.1	The carbonyl group	106
8.2	Nucleophilic attack on acyclic carbonyl compounds	110
8.2.1	Cram's rule	110
8.2.2	The Felkin-Ahn rule	111
8.3	Locking effects in nucleophilic reactions at carbonyl groups	113
8.4	The aldol reaction	114
	Answers to questions	116
9	STEREOCHEMISTRY OF SOME IMPORTANT REACTIONS LEADING TO THE FORMATION OF ALKENES	119
9.1	Elimination reactions	119
9.2	Wittig and related reactions	125
9.3	Reactions of sulfones	129
	Answers to questions	130
10	SOME REACTIONS OF SIMPLE ALKENES	133
10.1	Bromination reactions	133
10.2	Reactions involving osmium tetroxide	140
10.3	Epoxidation of alkenes	141
10.4	Reaction of alkenes with carbenes	142
	Answers to questions	144
11	SOME IMPORTANT CYCLIZATIONS INVOLVING PERICYCLIC REACTIONS	146
11.1	Diels-Alder reactions	146
11.2	Cycloadditions involving an alkene and a ketene	152
11.3	Electrocyclic reactions	154
	Answers to questions	159
12	CYCLIZATION REACTIONS THAT PROCEED THROUGH HIGH ENERGY INTERMEDIATES	161
12.1	Intramolecular attack by a nucleophile	161
12.2	Cyclizations involving carbocations	166
12.3	Radical-based cyclizations	166
	Answers to questions	170

### 13 STEREOCHEMISTRY OF SELECTED POLYMERS 171

13.1 Synthetic polymers 171

13.2 Proteins 172

13.3 Carbohydrates 179

13.3.1 Nucleic acids 180

Answers to questions 185

### 14 STEREOCHEMISTRY AND ORGANIC SYNTHESIS 186

14.1 Introduction 186

14.2 Using materials from the chiral pool 188

14.3 Using classical resolution techniques 194

Answers to questions 200

### 15 ASYMMETRIC SYNTHESIS 202

15.1 Chiral auxiliaries 202

15.1.1 Using an iron carbonyl as a chiral auxiliary:  
synthesis of Captopril 203

15.1.2 Using heterocycles as chiral auxiliaries: alkylation and  
hydroxyalkylation of propanoic acid 204

15.1.3 Camphor-derived chiral auxiliaries: Diels–Alder reaction 209

15.2 Chiral reagents 211

15.2.1 Asymmetric hydroboration reactions 211

15.2.2 Asymmetric reducing reagents related to lithium  
aluminium hydride and sodium borohydride 213

15.3 Chiral catalysts 214

Answers to questions 225

### 16 TOTAL ASYMMETRIC SYNTHESIS OF PROSTAGLANDIN $F_{2\alpha}$ AND COMPACTIN 227

16.1 Syntheses of prostaglandin  $F_{2\alpha}$  ( $PGF_{2\alpha}$ ) 227

16.1.1 Classical resolution of a  $PGF_{2\alpha}$  intermediate 229

16.1.2 Using chiral auxiliaries and optically active reagents 229

16.1.3 Synthesis of  $PGF_{2\alpha}$  starting with a natural product  
from the 'chiral pool' 233

16.1.4 Synthesis of primary prostaglandins using enzymes  
as chiral catalysts 234

16.2 Synthesis of compactin 236

Answers to questions 241

### APPENDIX 1 243

### APPENDIX 2 244

### INDEX 247

# 1 Shapes of simple molecules

## 1.1 Methane

The hydrocarbon methane is the simplest organic molecule. It contains four equivalent carbon–hydrogen bonds and its shape has been shown by various spectroscopic methods to be that of a regular tetrahedron (Fig. 1.1). The carbon sits in the centre of the tetrahedron and hydrogen atoms take up positions at the vertices.



Fig. 1.1

The shape of a molecule is determined by the electrons in the constituent atoms, both those which participate in chemical bonds and those which are non-bonding. The electron configurations of a number of atoms commonly encountered in organic chemistry are given in Table 1.1. If we consider the lowest energy (ground state) electron configuration of carbon,  $1s^2 2s^2 2p^2$ , the very formation of methane would appear to be anomalous. The three 2p orbitals ( $2p_x$ ,  $2p_y$ ,  $2p_z$ ) are able to accommodate a maximum of six electrons as three pairs of opposite spin. However, according to Hund's rule, when there are three or fewer electrons to accommodate spin pairing does not occur. In the case of carbon with two 2p electrons the two electrons enjoy sole occupation of two of the three p orbitals. From this it would look as if carbon should be divalent

Table 1.1 Electron configuration of some elements.

Element	Electron configuration
H	$1s^1$
C	$1s^2 2s^2 2p^2$
N	$1s^2 2s^2 2p^3$
O	$1s^2 2s^2 2p^4$
P	$1s^2 2s^2 2p^6 3s^2 3p^3$
S	$1s^2 2s^2 2p^6 3s^2 3p^4$

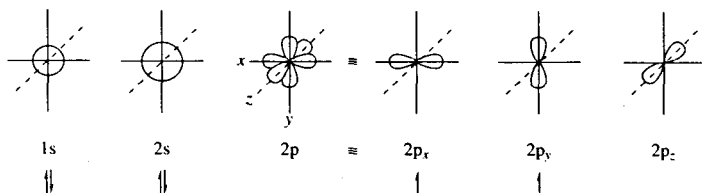
(since it apparently has only two electrons available for covalent bonding), but we know from the chemistry of carbon that it is in fact tetravalent, as in methane.

## 1.2 Hybridization

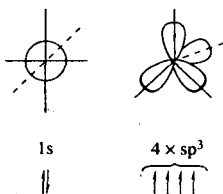
The explanation proposed to account for the tetravalency of carbon is based on the concept of hybridization. In this model the four valence electrons of carbon occupy four energetically equivalent (degenerate)  $sp^3$  orbitals which, as the name suggests, are 'hybrids' of the 2s and 2p originals. The hybrids are directed towards the vertices of a regular tetrahedron, and the angle between each pair of hybrids is  $109.5^\circ$ , which coincidentally is the angle of maximum separation.

Unlike the p orbitals, which are symmetrical in shape and which can accommodate the electron in either lobe with equal probability, the hybrid orbitals are highly unsymmetrical with a much greater probability of accommodating the electron in the large lobe. For convenience, conventional representations usually show only the large lobes (Fig. 1.2).

(a) Before hybridization



(b) After hybridization



(c)

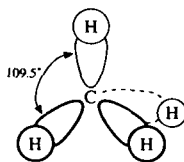


Fig. 1.2 Representation of orbitals before and after hybridization and the bonding orbitals of methane.

## 1.3 Ethene and ethyne

$sp^3$  Hybridization accounts for the tetrahedral shape of the carbon atoms in all saturated organic compounds. But what about compounds with double and triple bonds such as ethene (ethylene) and ethyne (acetylene)? Physical techniques have demonstrated that these molecules are planar and linear, respectively (Fig. 1.3).

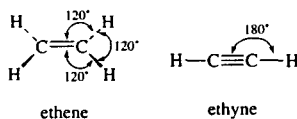


Fig. 1.3

Again, recourse is taken to the concept of hybridization but this time not all of the p orbitals are involved. In the ethene molecule, each of the carbon atoms has undergone  $sp^2$  hybridization; that is, the 2s and only two of the 2p orbitals of the original configuration have combined to give three degenerate  $sp^2$  orbitals and one remaining 2p orbital, Fig. 1.4. The calculated arrangement of the new orbitals is trigonal (angle =  $120^\circ$ ), which also provides the maximum separation.

(a) Before hybridization

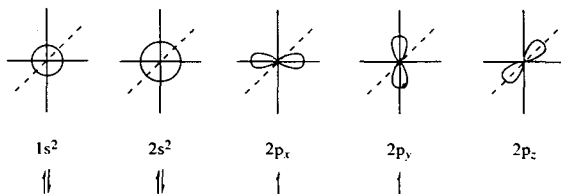
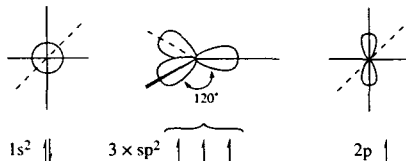
(b)  $sp^2$  hybridization

Fig. 1.4

The  $sp^2$  orbitals again have characteristics of both 'parent' s and p orbitals but there are differences between the shapes of the  $sp^2$  and  $sp^3$  lobes;  $sp^2$  orbitals have more 's' character than their  $sp^3$  counterparts (33.3% compared with 25%) and so have rounder, shorter lobes.

The term 'double bond' is a poor descriptor of the alkene unit, particularly when used with conventional structural formulae which tend to show alkenic bonds as two equally contributing bonds. This is not the case: a double bond comprises a strong  $\sigma$ -bond and a weaker  $\pi$ -bond. Figure 1.5 shows how a double bond is constructed.

The  $\sigma$ -bond is formed by direct end-on overlap between one of the  $sp^2$  orbitals on each of the carbon atoms. The  $\pi$ -bond, on the other hand, is formed by weaker, sideways overlap between the two p orbitals, one on each carbon. Such

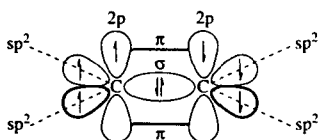


Fig. 1.5

lateral overlap is all that the p orbitals can manage, because the p orbital is placed orthogonally (perpendicularly, zero overlap) to the  $sp^2$  hybrids in the plane and the result is a molecular orbital consisting of a ' $\pi$ -cloud' above and below the plane of the  $\sigma$ -bond. The remaining  $sp^2$  orbitals  $\sigma$ -bond with hydrogen or other substituents.

Finally, similar treatment gives us the structure of ethyne, which has one strong  $\sigma$ -bond and two weak  $\pi$ -bonds. Hybridization in this case involves only one of the 2p orbitals and the 2s orbital, Fig. 1.6 ( $sp$  hybridization). The  $sp$

(a) Before hybridization

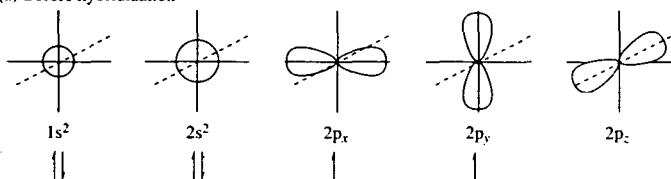
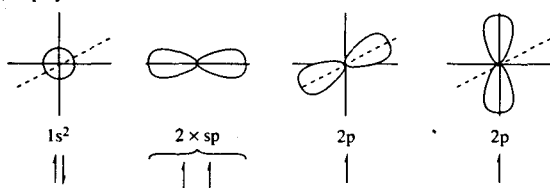
(b)  $sp$  hybridization

Fig. 1.6

orbitals have 50% 's' character and are rounder and shorter still, and, as before, engage in end-on overlap to make a strong  $\sigma$ -bond, Fig. 1.7. As there are only two  $sp$  orbitals, each containing an electron, they become linearly disposed and the  $180^\circ$  angle affords maximum separation. The two remaining

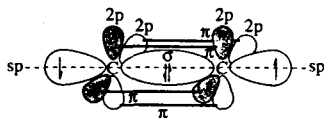


Fig. 1.7

orthogonal p orbitals on each carbon atom participate in weaker sideways overlap above and below, and in front and behind the axis of the  $\sigma$ -bond. The decrease in bond length as we proceed from ethane (1.54 Å) through ethene (1.33 Å) to ethyne (1.20 Å) reflects the increased amount of bonding between the carbons and the increase in 's' character of the central  $\sigma$ -bond.

## 1.4 Molecules containing elements other than carbon

The hybridization model can also be applied to other elements that are frequently encountered in organic chemistry. Amines, ethers and water, although possessing less than four ligands, nevertheless are approximately  $sp^3$  hybridized species.

The electron configuration of nitrogen is  $1s^2 2s^2 2p^3$ , therefore the  $sp^3$  orbitals resulting from hybridization of the 2s and 2p orbitals are required to accommodate five electrons. Nitrogen does this by placing a single electron in three of the four lobes and a pair of electrons in the remaining lobe. Thus the lone pair becomes the fourth 'ligand' and the tetrahedral arrangement is again assumed. The effectively large volume required by the lone pair, compared with the bonding electrons, means that the ligands are not disposed in quite a regular tetrahedral fashion and there is a certain amount of deviation from the normal  $109.5^\circ$  angle (for example, the H—N—H angle in  $NH_3$  is  $106.8^\circ$ , Fig. 1.8).

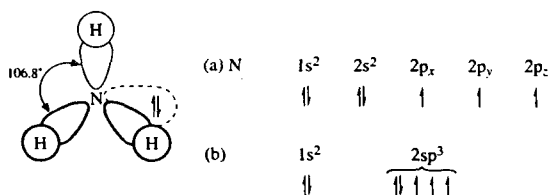


Fig. 1.8

The tetrahedral arrangement in amines and ammonia is by no means static: the lone pair is able to migrate to the other face of the molecule causing the configuration to flip or invert to give the mirror image (Fig. 1.9). However, the energy barrier associated with this process is very small and the inversion occurs much too rapidly for either of the two forms to be isolated (for example, ammonia is estimated to undergo  $2 \times 10^{11}$  inversions per second, and has an inversion energy  $E_{inv}$  of  $23 \text{ kJ mol}^{-1}$ ).

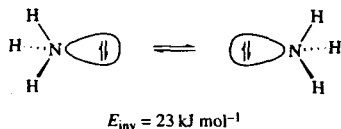
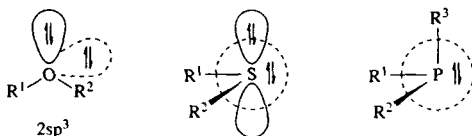


Fig. 1.9



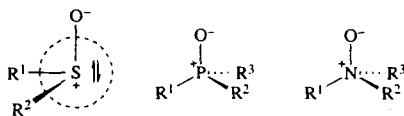
This is not so with the phosphorus analogues, called phosphines. Phosphorus, a third-row element, has the electronic configuration  $1s^2 2s^2 2p^6 3s^2 3p^3$  and here hybridization between the 3s and 3p orbitals is not very effective. Therefore we have three singly occupied p orbitals, which form bonds with other ligands, and one doubly occupied s orbital (the lone pair). The barrier to inversion in phosphines is much higher than in amines, so much so that inversion takes place only at higher temperatures ( $E_{\text{inv}} = 113 \text{ kJ mol}^{-1}$ ).

Ethers and water are also approximately tetrahedral: in oxygen (electron configuration  $1s^2 2s^2 2p^4$ ) the valence shell is hybridized to  $2sp^3$  with two of the lobes occupied by two lone pairs of electrons. The situation for  $\text{H}_2\text{S}$  and sulfides is akin to that for phosphines. Thus bonds are made to singly occupied p orbitals, lone pairs of electrons occupying the 3s and orthogonal 3p orbital.



**Fig. 1.10** The approximately tetrahedral structures of ethers and water (the  $\text{H}-\text{O}-\text{H}$  bond angle in water is  $104.5^\circ$ ) and the shape of sulfides and phosphines.

The electronegative oxygen atom exerts a very tight grip on the two pairs of non-bonding electrons. However, nitrogen and phosphorus, being less electronegative, are able to undergo oxidation by donation of one of the lone pairs to give, for example, amine oxides and phosphine oxides, respectively. Each species now has four separate ligands, which lock the tetrahedral structure and prevent inversion. Sulfur can also donate one of its lone pairs to form sulfoxides, in which the remaining lone pair is one of the ligands. If each of the ligands is different, i.e.  $\text{R}^1 \neq \text{R}^2 \neq \text{R}^3$  (Fig. 1.11), then the oxides display chirality, the stereochemical consequences of which can be very important. A fuller discussion of chiral compounds is given in Chapter 2.



**Fig. 1.11** Representations of sulfoxides, phosphine oxides and amine oxides. In phosphine oxides the requirement to form a fourth bond overcomes the reluctance of 3s and 3p orbitals to hybridize (cf. phosphines). The hybridization in the phosphine oxides approximates to  $sp^3$  and the bond angles are close to tetrahedral.

This  $sp^2$  hybridization accounts for the shapes of ketones, thiones and other carbonyl-containing compounds, imines, oximes and azo-containing molecules. Nitriles are  $sp$  hybridized (Fig. 1.12).