Ruthenium Oxidation Complexes

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RUTHENIUM OXIDATION COMPLEXES

Volume Author

W.P. Griffith
Department of Chemistry
Imperial College
London, SW7 2AZ
United Kingdom

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Prof. William P. Griffith

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Their Uses as Homogenous Organic Catalysts

Springer

Prof. William P. Griffith
Department of Chemistry
Imperial College
London, SW7 2AZ
United Kingdom
w.griffith@imperial.ac.uk

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Preface

This book is concerned with the application of ruthenium complexes as catalysts for useful organic oxidations.

Ruthenium was the last of the platinum-group elements to be discovered, and has perhaps the most interesting and challenging chemistry of the six. In this book just one major aspect is covered: its ability, mainly by virtue of its remarkably wide range of oxidation states which exist in its many complexes (from +8 to −2 inclusive) to effect useful and efficient oxidations of organic substrates.

Emphasis has been placed on useful organic oxidations, particularly on the catalytic production of natural products or pharmaceuticals and of the oxidation of important organic functional groups such as alcohols, alkenes, alkynes, amines and heteroatomic functionalities. The book is not directed solely at organic chemists. It is hoped that the inorganic, organometallic and coordination chemist will draw from it useful information, particularly from Chapter 1. The coverage of this very large subject can not claim to be entirely comprehensive, but it is hoped that all the main references, including some from 2010, have been covered.

The first chapter concerns the chemistry of the oxidation catalysts, some 250 of these, arranged in decreasing order of the metal oxidation state (VIII) to (0). Preparations, structural and spectroscopic characteristics are briefly described, followed by a summary of their catalytic oxidation properties for organic substrates, with a brief appendix on practical matters with four important oxidants. The subsequent four chapters concentrate on oxidations of specific organic groups, first for alcohols, then alkenes, arenes, alkynes, alkanes, amines and other substrates with hetero atoms. Frequent cross-references between the five chapters are provided.

I would like to thank my good friend Brian James of the University of British Columbia (UBC), who suggested some years ago that I write a book of this type and who has carefully read and trenchantly criticised large sections of it. From Imperial College I am deeply indebted to Ed Smith who has read all of it and pointed out a number of errors and inconsistencies, and Ed Marshall who has drawn all the figures. I am very grateful to Steve Ley from Cambridge who has read the section on TPAP, the reagent which he, I and our co-workers developed. Any remaining errors and omissions are entirely my responsibility. All the cited references have of course been consulted and, though most are from online sources, it

is a pleasure to thank the librarians of Imperial College, the Science Museum and the Royal Society of Chemistry libraries, and of course of the British Library. Finally, I am deeply grateful to my wife Anne (and in earlier years to my daughters Helen and Miranda) for her forbearance during the long time this book has taken to compile.

Contents

Abbreviations

Abbreviations which are commonly used in the book are listed here: each is defined when it first occurs in the text, but not subsequently; those used once only are not listed here. Wherever possible internationally known abbreviations (e.g. bpy, py, etc.) are used, but in some cases the usage of the authors of the papers cited have been used.

acac	Acetylacetonate mono-anion (2,4-pentanedionate mono-anion)
atm	Atmospheres (pressure)
aq.	In aqueous solution, or aquated
BHT	2,6-di-*tert*-Butyl-4-methylphenol
B.M.	Bohr magnetons
Bmim	1-Butyl-3-methylimidazolium mono-cation
Bn	Benzyl, $C_6H_5CH_2$
Boc	*tert*-Butoxycarbonyl
bpy	2,2′-Bipyridyl
BDTAC	Benzyldimethyltetradecylammonium chloride
BTBAC	Benzyltributylammonium chloride
BTEAC	Benzyltriethylammonium chloride, $(PhCH_2NEt_3)Cl.H_2O$
Bu	Butyl
^{t}Bu	*tert*-Butyl
Bz	Benzoyl, C_6H_5CO
Ch.	Chapter
CHP	Cumene hydroperoxide
cinc	Cinchomeronate (3,4-pyridinedicarboxylate dianion)
COD	Cyclo-octa-1,5-diene
Cp	π-C_5H_5 Mono-anion
Cp*	η^5-C_5Me_5 Mono-anion
Cl_2bpy	6,6′-Dichloro-2,2′-bipyridyl
Cl_2pyNO	2,6-Dichloropyridine-*N*-oxide
DCE	1,2-Dichloroethane
DDAB	Didecyldimethylammonium bromide
DFT	Density function theoretical (calculations)

DMF	Dimethylformamide
dmg	Dimethylglyoxime mono-anion
dmp	2,9-Dimethyl-1,10-phenanthroline
DMSO, dmso	Dimethylsulfoxide (upper case for solvent, lower-for ligand)
dpae	1,2-bis-(Diphenylarsino)ethane
dppe	1,2-bis(Diphenylphosphino)ethane
dppp	1,3-bis(Diphenylphosphino)propane
dppm	bis(Diphenylphosphino)methane
ε	Molar extinction coefficient,/ $dm^3\ mol^{-1}\ cm^{-1}$
EDTA	Ethylenediaminetetra-acetate tetra-anion $EDTA^{4-}$ (acid is H_4EDTA; Fig. 1.33)
e.e.	Enantiomeric excess
emim	1-Ethyl-3-methy l-1H-imidazolium mono-cation
ESR	Electron spin resonance
Et	Ethyl
EtOAc	Ethyl acetate
h	Hours
Hx	*n*-Hexyl
IR	Infrared
M	Molar
MCPBA	Metachloroperbenzoic acid or 3-chloroperbenzoic acid
Me	Methyl
mech.	Mechanism
Me_2CO	Acetone
MTCAC	Methyltricaprylammonium chloride
μ_{eff}	Magnetic moment in Bohr Magnetons at room temperature
(N)	Nitride (N^{3-}) ligand
napy	1, 8-Naphthyridine
$\upsilon^{as}(Ru(O)_2)$	Asymmetric IR or Raman stretching vibration of an RuO_2 unit
$\upsilon^{s}(Ru(O)_2)$	Symmetric IR or Raman stretching vibration of an RuO_2 unit
υ (Ru=(O))	Stretching vibration of an Ru=O unit
nic	Nicotinate dianion
NMO	N-methylmorpholine-*N*-oxide
n.o.	Not observed
(O)	Oxo (O^{2-}) ligand
OAc	Acetate
OEP	2,3,7,8,12,13,17,18-Octaethylporphyrinate dianion
ox	Oxalate, $(C_2O_4)^{2-}$
Oxone®	$2KHSO_5.\ KHSO_4.K_2SO_4$
Pc	4,4,′4,′′′4′′′′-Tetrasulfophthalocyaninate dianion
PCB	Polychlorinated biphenyls

PDTA	Propylenediamine tetra-acetate tetra-anion, $PDTA^{4-}$
Ph	Phenyl, C_6H_5
phen	1,10-Phenanthroline
pic	Picolinate (2-pyridinecarboxylate dianion)
PMS	Powdered (4 Å) molecular sieves
PNAO	Poly-*N*-methylmorpholine-*N*-oxide
PPN	$(Ph_3P)_2N)^+$
Pr	Propyl
^{i}Pr	Isopropyl
py	Pyridine
pydic	Pyridine-2,6-dicarboxylic acid
pyNO	Pyridine *N*-oxide
PS-TPAP	Polymer-supported TPAP
R	Raman spectrum
RT	Room temperature
SB	Schiff's base
SCE	Standard calomel electrode
stoich.	Stoicheiometric
Tet-Me_6	*N, N, N′, N′,* 3, 6-Hexamethyl-3,6-diazaoctane-1,8-diamine
TBAP	Tetra-*n*-butylammonium perruthenate, $(^nBu_4N)[RuO_4]$
TBHP	*tert*-Butylhydroperoxide, ^{t}BuOOH
TCCA	Trichloroisocyanuric acid
TDCPP	*meso*-5,10,15,20-*tetrakis*(2,6-Dichlorophenyl)porphyrin dianion
TEMPO	2,2′,6,6′-Tetramethylpiperidine-N-oxyl radical (Fig. 1.40)
$TFPPCl_8$	Octachloro*tetrakis*(pentafluorophenyl)porphyrinate dianion
TGA	Thermal gravimetric analysis
THF	Tetrahydrofuran
TMC	Tetramethyl-tetra-azacyclotetradecane (Fig. 1.29)
TMEA	*N,N,N′,N′*- Tetramethyl-1,2-diaminoethane
tmeda	*N, N, N′, N′*-tetramethylethylenediamine
TMP	*meso*-5,10,15,20-Tetramesityl(porphyrinate) dianion (Fig. 1.24)
TMPZNO	Tetramethylpyrazine-*N,N′* dioxide
tmtacn	1,4,7-Trimethyl-1,4,7-triazacyclononane (Fig. 1.30)
tpa	Tris(2-pyridylmethyl)amine)
TPAP	Tetra-*n*-propylammonium perruthenate, $(^nPr_4N)[RuO_4]$
TPAP/NMO	Oxidising mixture of TPAP and NMO
TPAPORM	TPAP doped on ormosil silica glass
TPP	*meso*-5,10,15,20-Tetraphenyl(porphyrin)ate dianion
Troc	Trichloroethoxycarbonyl
TTP	Tetramesitylporphyrinate dianion
tpy	2,2′:6′,2″-Terpyridine
UV	Ultra-violet (irradiation)
v	Volts

Chapter 1
The Chemistry of Ruthenium Oxidation Complexes

Abstract This chapter introduces the topic and scope of the book and principally concerns the basic preparation, physical and chemical properties of Ru-based oxidation catalysts, then summarising the catalytic oxidations which they accomplish. More detail on these is given in the succeeding four chapters. The major oxidants RuO_4 (1.2.1), perruthenate $[RuO_4]^-$ (1.3.1) – mainly TPAP, $(^nPr_4N)[RuO_4]$, ruthenate $[RuO_4]^{2-}$ (1.4.1), trans-$Ru(O)_2$(TMP) (1.4.2.5), $RuCl_2(PPh_3)_3$ (1.9.3) and cis-$RuCl_2(dmso)_4$ (1.9.4) are covered in some detail, but many other catalysts are also discussed. In some cases brief comments are made on the mechanisms involved when data on these are given in the cited papers. There is also an Appendix (1.11) which gives brief details on the preparation of four ruthenium oxidation catalysts and selected model oxidations using them.

1.1 Overview and Introduction

This chapter is essentially a review of those ruthenium complexes which have been used as oxidation catalysts for organic substrates, emphasis being placed on such species which have been chemically well-defined and are effective catalysts. Of all the ruthenium oxidants dealt with here those which have the greatest diversity of use are RuO_4, $[RuO_4]^-$, $[RuO_4]^{2-}$, the tetramesityl porphyrinato (TMP) complex *trans*-$Ru(O)_2$(TMP), $RuCl_2(PPh_3)_3$, and *cis*-$RuCl_2(dmso)_4$. Many other catalysts are covered, and the uses of two principal starting materials, $RuO_2.nH_2O$ and $RuCl_3.nH_2O$ as precursors for a number of catalysts, discussed.

The material is arranged under the formal oxidation state of the ruthenium in the complexes, in descending order within each category, *viz.* Ru(VIII) to Ru(0). Individual complexes within each oxidation state are covered and for each, wherever possible, references to preparation, structural and basic physico-chemical data are given. The arrangement of complexes within each oxidation state broadly follows the sequence of donor atoms used in the book: O, N, P, As, Sb, S, C. Within each formulation ligands determining the oxidation state are placed first (e.g. (O), (N), F, Cl, Br, I, (acac) etc.), e.g. *cis*-$RuCl_2(phen)_2$) rather than *cis*-$Ru(phen)_2Cl_2$.

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In general ligands are listed in order of increasing denticity within a complex, e.g. $[Ru(H_2O)(bpy)(tpy)]^{2+}$ rather than $[Ru(tpy)(H_2O)(bpy)]^{2+}$.

Oxidations of organic substrates by these species are then briefly considered for classes of organic substrates. Both in this and in subsequent chapters these are arranged in the order: alcohols (including carbohydrates), alkenes, arenes, alkynes, alkanes, amines, amides, ethers, sulfides, phosphines, arsines and stibines; and finally miscellaneous oxidations not covered in preceding sections. Tables of typical oxidations are given in Chapters 2–5; within these tables oxidation products are arranged alphabetically in the central column. In a few cases stoicheiometric oxidants are covered where it is likely that such reactions might be rendered catalytic; occasionally species which show potential catalytic or stoicheiometric oxidative properties are mentioned. Electrocatalytic oxidations are covered but not heterogeneous catalysis not patented procedures, though a few instances of supported catalysis are mentioned. Since the book concentrates on practical usage of the catalysts, the coverage of reaction mechanisms is deliberately light, though references are given wherever possible.

At the head of most of the oxidation sections in Chapters 2–5 a very simplified overall equation is given for the specified set of reactions, its purpose being merely to indicate the notional overall stoicheiometry of the reaction. In these [O] indicates the input of one oxygen atom, 2[O] of two, etc. from the oxidant; there being no mechanistic implications in these simplistic equations. For oxidations of a given organic substrate to the organic product the relation between a Ru starting material (assumed in this case to be an oxoruthenate) is generalised as $Ru^{N}O_x$ with $Ru^{N+2}O_{x+1}$ (two-electron oxidation) or $Ru^{N+4}O_{x+2}$ (four-electron oxidation) as the likely catalyst or catalyst precursor. In Fig. 1.1 the example given is of $Ru^{IV}O_2$ and its four-electron oxidation product $Ru^{VIII}O_4$.

In this and subsequent chapters the rubric:

Starting Ru material/co-oxidant/solvent/temperature (if not ambient) is used. Thus Fig. 1.1 would be written in the text as RuO_2/aq. $Na(IO_4)$, meaning that RuO_4 is generated *in situ* from $RuO_2.nH_2O$ and aqueous sodium periodate (only non-ambient temperatures would appear in the rubric). Biphasic solvent mixtures with water are denoted as water-solvent.

Most of the Ru(VIII) to Ru(IV) complexes featured are oxoruthenates; although those of Ru(III), (II) – e.g. $RuCl_2(PPh_3)_3$ – and Ru(0) do not lie in this category,

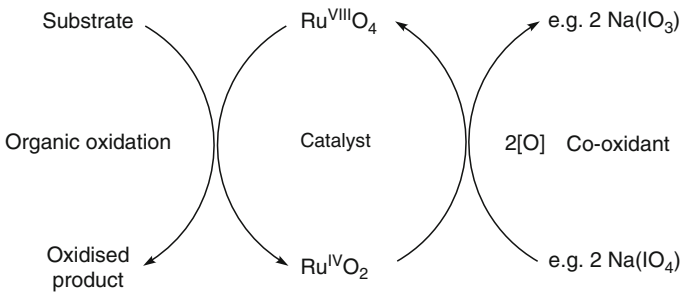

Fig. 1.1 Simple scheme for oxoruthenate oxidation catalysis

oxoruthenates may well be intermediates in their oxidation reactions. The modern convention of bracketing co-ordinated oxo ligands O_2^{2-} as (O) is followed except for the homoleptic RuO_4, $[RuO_4]^-$, $[RuO_4]^{2-}$ species, RuO_2 and polyoxometalates. The precursors mainly used in ruthenium oxidation catalysis are the hydrated dioxide $RuO_2.nH_2O$ and particularly the hydrated trichloride $RuCl_3.nH_2O$; for brevity throughout the text these are referred to simply as RuO_2 and $RuCl_3$. Such reactions are much more effective if carried out with the hydrated materials than with the anhydrous forms.

In a work of this length the use of abbreviations is essential. If an abbreviation is used in one paragraph only (as is the case for some complex ligands) it is defined in that paragraph alone.

1.1.1 Discovery of Ruthenium

Ruthenium was the last of the six platinum group metals to be isolated, and was discovered in Kazan (now capital of the Tatarstan Republic, Russian Federation) by Karl Karlovich Klaus[1] (1796–1864) in 1844. The original papers were published in Russian journals which are difficult to obtain now, but were published in Western Europe in 1845 [1, 2] with a summary in English [3]. Klaus made the metal by reduction of RuO_2 with H_2 and named it Ruthenium in honour of his native land (*Ruthenia*, Latin for Russia); there are short biographies of him [4, 5].

Gottfried Wilhelm Osann (1797–1866) discovered what he thought was a new element in 1827 and named it 'Ruthenium' but his claim is generally discounted [6, 7] though he still has some supporters [8]. Klaus was the first to make RuO_4, *trans*-$K_2[Ru(OH)_2(O)_3]$ (which he regarded as $K_2[RuO_4].H_2O$), RuO_2 and $RuCl_3$, all essential players in Ru oxidation chemistry. He assigned to ruthenium an atomic weight of 102.4 based on the $Na_3[RuCl_6]/H_2$ reaction [9], later raising this to 104 [10]. The modern IUPAC recommended value for Ru is 101.07(2) [11], and its atomic number is 44.

1.1.2 Oxidation States in Ruthenium Complexes

Ruthenium and osmium are unique amongst all known metallic elements in three respects. Firstly they alone form octavalent homoleptic oxo complexes, RuO_4 and OsO_4. Secondly, complexes of these metals containing one of the eleven oxidation states theoretically available to transition metals are known, from M(VIII) to M(-II) inclusive (M=Ru, Os), corresponding to electron configurations of d^0 to d^{10}. Good σ-donors such as F^-, O^{2-} and N^{3-} stabilise higher oxidation states while effective π-acceptors such as CO and NO^+ stabilise low oxidation states. The oxo ligand O^{2-}, the complexes of which concern us in this book, stabilises five oxidation states of Ru (VIII) to (IV) inclusive as a terminal ligand and four (VI to III) inclusive as a bridging

[1] K. K. Klaus appears as C. Claus in the early German publications, which are cited here since they are more accessible than the Russian originals.

ligand. It is this very wide range of oxidation states, mostly of course in conjunction with suitable co-ligands, and a generally favourable balance of kinetic lability and stability which allows so much oxidation chemistry to be carried out with ruthenium. By choosing suitable co-ligands it is possible to change the redox characteristics of the ruthenium centre and so in effect to adjust the oxidation properties of the catalyst.

1.1.3 Reviews on Ruthenium Complexes in Oxidation Reactions

There is no previous review or book of the type presented here, but there are some very useful reviews on its general chemistry. The two classic volumes by Gmelin in 1970 [12] and in 1938 [13] are invaluable for the early work, as are the magisterial bibliographies by Howe covering the period 1844–1950 [14–16]. The Seddons' admirably comprehensive book on the element, *The Chemistry of Ruthenium*, covers material up to 1983 [6] and the author's book *The Chemistry of the Rarer Platinum Metals (Os, Ru, Ir and Rh)* does so to 1967 [17]; less comprehensive but still useful is Simon Cotton's *Chemistry of Precious Metals* [18]. There are reviews on higher [19–21] and lower [22] oxidation state complexes of the element. The *Encyclopedia of Inorganic Chemistry* has useful articles on its coordination and organometallic chemistry respectively [23, 24].

There is no single publication covering oxidations by ruthenium[2] complexes as presented in this book. However there are some fairly general reviews, and also more specific ones which will be mentioned in the relevant parts of the text. Here we list only those which apply to Ru oxidants in general: [25–27]; biomimetic Ru oxidations [28, 29]; a book on *Ruthenium in Organic Synthesis* has a chapter on oxidations [30]; a review on large-scale oxidations in the pharmaceutical industry include some Ru-catalysed examples [31]. There are broad reviews on Ru complexes in organic synthesis [32]; on Ru oxo complexes as organic oxidants [33–36]; reviews on platinum-group metal oxidations including Ru [37–40]; oxidations by Ru porphyrin species [41–47] and by Ru macrocyclic complexes [48]. There are also reviews as part of more general treatments of oxidation by metal-oxo species [49–51]; on 'green' oxidations involving O_2 and H_2O_2 [52] and on O_2 [47, 52–54] as co-oxidants. For reviews on RuO_4 *cf.* 1.2.1 below and for TPAP *cf.* 2.1.2.

1.1.4 Reviews on Oxidations of Organic Substrates by Ru Complexes

These are included in the following chapters but are grouped together here. They include oxidations of *alcohols* in Ch. 2, a prime target for Ru-catalysed oxidations

[2] Henceforth in most cases abbreviated as Ru.

[19, 25–27, 29, 30, 35, 53–60]. In Ch. 3 are considered *alkenes* for which Ru complexes are active in epoxidation reactions [27, 30, 35, 60–62], including asymmetric epoxidations [44, 63]; *cis*-dihydroxylations [64–67]; ketohydroxylations [28, 64, 66, 67]; alkene cleavage reactions [38, 50, 65, 68, 69, 71], *arenes* [27, 28], and *alkynes* [60, 65, 70, 71]. In Ch. 4 Ru-catalysed oxidations of *alkanes* are covered: [19, 27, 30, 51, 72]. Finally in Ch. 5 oxidation of a series of heteroatomic substrates is considered: *amines* [27, 28, 30, 32, 42, 73, 74]; *β-lactams and amides* [27, 30]; *ethers* [35, 47]; *sulfides* [42, 46, 47]; *phosphines, arsines and stibines* [46, 47], and finally those few substrates which do not fall under the categories above.

1.1.5 Syntheses of Natural Products or Pharmaceuticals by Ru Catalysts

Many biologically important materials have been synthesised by using Ru catalysts as part of multi-step syntheses. The catalyst used is indicated in parentheses. These include essential steps in synthesis of the phytohormone Abscisic acid (TPAP) [75]; the marine eicosanoid Agardhilactone (TPAP) [76]; the sugar D-allose (RuO_4); Fig. 2.13, [77]; the hormone *d*-Aldosterone (RuO_4) [78, 79]; the antitumour styryllactone (+)-Altholactone (TPAP) [80]; the macrolide Altohyrtin A (TPAP) [81]; the quassinoid (±)-Amarolide (RuO_4) [82]; the fragrance (−)-Ambrox® (RuO_4 and $[RuO_4]^-$) (Fig. 3.20) [83]; the marine macrolide Amphidinolide T1 (TPAP) [84]; the immunosuppressive agent Antascomicin B (TPAP) [85]; the marine natural product Antheliolide A (TPAP) [86]; the plant hormone (±)-Antheridiogen (A_{An}, 2) ($[RuO_4]^{2-}$) [87]; the non-proteinogenic amino acid Anticapsin (TPAP) (Fig. 2.7) [88, 89]; the cytotoxic benzolactone enamide Apicularen A (TPAP) [90]; the sugar D-Arcanose (RuO_4) [91]; the anti-malarial agent Arteether (TPAP; Fig. 2.4) [92]; the AChE inhibitor (+)-Arisugacin A and B (TPAP) [93]; the eunicellin Astrogorgin (TPAP) [94]; the anti-parasitic Avermectin-B1a (TPAP; Fig. 2.6, 1.11) [95–97]; the antifeedant and growth-disruption agent Azadirachtin (TPAP) [98–100]; the alkaloid (+)-Batzelladine A (TPAP; Fig. 1.13) [101]; the antibiotic Biphenomycin B (RuO_4) [102]; the antibiotic (−)-Borrelidin (TPAP) [103]; the neurotoxin Brevetoxin B (TPAP) [104, 105]; the limonoid Calodendrolide (TPAP) Fig. 2.8) [106]; the pheromone *R*-γ-Caprolactone (RuO_4) [107]; the nutritional supplement L-Carnitine (RuO_4) [108]; the antiviral Castanospermine and 1-Epicastanospermine (TPAP) [109]; the vinca alkaloid (+)-Catharanthine (TPAP) [110]; the sesquiterpene (−)-Ceratopicanol (RuO_4, TPAP) [111]; the sugar L-Cladinose (RuO_4) [112, 113]; the antitumour agent *ent*-Clavilactone B (TPAP) [114]; the synthase inhibitor (−)-CP-263,114 (TPAP) [115]; the biologically active sequiterpene (−)-Diversifolin (TPAP) [116]; the sesquiterpene isoDrimeninol ($[RuO_2Cl_3]^-$) [117]; the agonist Dysiherbaine (TPAP) [118]; the marine anti-tumour agent Eleutherobin (TPAP) [119]; the analgesic (±)-Epibatidine (TPAP) [120]; the anti-growth factor 2-Epibotcinolide (TPAP) [121]; the cytotoxic (−)-7-Epicylindrospermopsin (TPAP) [122]; the carbohydrate 1-*epi*Hyantocidin (TPAP) [123]; the alkaloid (±)-Epimaritidine (TPAP) [124]; the cytotoxic antitumour

agent Epothilone C (TPAP) [125]; the antileukemic agents (−)-Eriolangin and (−)-Eriolanin (TPAP) [126]; the spirobicyclic sesquiterpene (±)-Erythrodiene (TPAP) [127]; the enzyme inhibitor (+)-Fagomine (TPAP) [128]; the cytotoxic Fasicularin (TPAP) [129]; the anti-inflammatory Flurbiprofen (RuO_4) [130]; the limonoid Fraxinellone (TPAP) [131]; the polycyclopropane antibiotic FR-900848 (RuO_4) [132]; the plasmodial pigment Fuligorubin A (TPAP) [133]; the biologically active amino sugars Furanodictines A and B (TPAP) [134]; the antibiotic carbasugars Gabosine I and Gabosine G (TPAP) [135]; the antifungal Gambieric acids A and C (TPAP) [136]; the ether toxin Gambierol (TPAP) [137]; the growth factor Gibberellic acid ($[RuO_4]^{2-}$) [138]; the anti-cancer agent (+)-Goniodiol (TPAP) [139, 140]; the cytotoxic Gymnocin-A (TPAP) [141]; the steroidal phytohormone (22*S*, 23*S*)-28-Homobrassinolide (Fig. 3.5) (RuO_4) [142]; the acetogenin 10-Hydroxyasimicin (TPAP [143]; the xenicane diterpene 4-Hydroxydictyolactone (TPAP) [144]; the antibiotic *dl*-Indolizomycin (TPAP) [145]; the carbohydrate *allo*-Inositol (Fig. 3.3) (RuO_4) [146]; the antitumour agent Irisquinone (TPAP) (Fig. 2.3) [147]; the alkaloid (+)-Laccarin (RuO_4) [148]; the alkaloid (±)-Lapidilectine B (TPAP) [149]; the colony-stimulating factor Leustroducsin B (TPAP) [150]; the pheromone (±)-Lineatin (RuO_4) [151]; the antiparasitic spiroketal macrolides (+)-Milbemycin α_1 (TPAP) [152] and (+)-Milbemycin β_1 (TPAP) [153]; the cytotoxic sponge alkaloids Motopuramines A and B (TPAP) [154]; the acetogenin Muricatetrocin C (TPAP) [155]; the sugar L-Mycarose (RuO_4) [112, 113]; the pathogenetic agent Mycocerosic acid (RuO_4) [156]; the glutamate receptor Neodysiherbaine (TPAP) [157]; the antiviral nucleoside (−)-Neplanocin A (TPAP) [158]; the sesquiterpene Nortrilobolide (TPAP) [159]; the marine alkaloid Norzoanthamine (TPAP) [160]; the phosphatase inhibitor Okadaic acid (TPAP) [161]; the triterpene (+)-α-Onocerin (RuO_4) [162]; the eunicellin Ophirin B (TPAP) [94]; the antiviral (−)-Oseltamivir (RuO_4) [163, 164]; the anticarcinogen Ovalicin (TPAP) [165]; the alkaloid (±)-Oxomaritidine (TPAP) [166]; the biologically active diterpene Phonactin A (TPAP) [167]; the cytotoxic agent Phorboxazole (TPAP) [168]; the macrolide Prelactone B (TPAP) [169]; the antibacterial agent Pseudomonic acid C (TPAP) [170]; the sugar D-Psicose (RuO_4) [171]; the immunoadjuvant QS-21A_{api} (TPAP) [172]; the lipophilic maacrolide Rapamycin (TPAP) [173], *cf* 1.11, [174], (RuO_4) [175]; the antigenic diterpene (+)-Resiniferatoxin (TPAP) [176]; the antitumour macrolide (+)-Rhizoxin D (TPAP) [177]; the spiroketal ionophore antibiotic Routiennocin (TPAP) [178, 179]; the metabolites Salicylihalamines A and B (TPAP) [180]; the anti-tumour stablising agents Sarcodictyins A and B (TPAP) [181]; the polypropionate Siphonarienolone (TPAP) [182]; the microbial metabolite (+)-SCH 351448 (TPAP) [183]; the antitumour *cis*-Solamin (RuO_4, TPAP) [184]; the heliobactericidal (+)-Spirolaxine methyl ether (TPAP) [185]; the antimicrobial Squalamine (RuO_4) [186]; the anticancer drug Taxol® (TPAP) [187, 188]; the antibiotic and antiparasitic Tetronasin (TPAP) [189, 190]; the antiviral Tamiflu ((−)-Oseltamivir) (RuO_4) [163, 164]; the antitumour Tetronolide (TPAP) [191]; the coagulation protein Thrombin (RuO_4) [192]; the antibiotic (+)-Tetronomycin (TPAP) [193]; the SERCA inhibitors Thapsigargins (TPAP) [194–196]; the sesquiterpene Thapsivillosin F and Trilobolide (TPAP) [159]; the antitumour agent Tonantzitlolone (TPAP) [197]; the sesquiterpene Trilobolide (TPAP) [159];

the naturally occurring toxin Verrucarin A (RuO_4) [198]; the therapeutic hypercholesterolemia agent Zaragozic acid A (TPAP) [199], and the cholesterol biosynthesis inhibitor 1233A (TPAP) [200].

1.2 Ru(VIII) Complexes

The chemistry of Ru(VIII) is dominated by that of the tetroxide, RuO_4.

1.2.1 Ruthenium Tetroxide, RuO_4

This was the first oxidant of Ru to be discovered and is still one of the most important and versatile. The coverage here and in subsequent chapters of organic oxidations by this reagent does not claim to be fully comprehensive but it is hoped that most of the major applications have been included. It is perhaps the most celebrated compound of Ru as an oxidant, although it does in general lack selectivity in its oxidation reactions. Its CAS number is **20427-56-9**.

It is extensively used as an oxidant, mainly catalytically. There are good reviews on its oxidative properties: [12, 34–36, 39, 60, 64, 201–203]. Rylander's historic paper [71], Courtney [60] and Gore's [35] reviews, though early, are highly recommended, as is the article by Lee and van der Engh in 1973 which gives good experimental details for a number of organic oxidations by RuO_4 [203].

1.2.2 Preparation

Although Klaus discovered Ru in 1844 [1] it was not until 1860 that he isolated (and analysed) the volatile tetroxide, by passing Cl_2 into a solution of $Na_2[RuO_4]$ [10]. It is usually prepared *in situ* from a convenient Ru compound such as the trichloride or dioxide with a suitable oxidant, a procedure used in all but the earliest organic oxidations using RuO_4. The pure compound was made by boiling aqueous $RuCl_3$ with $Na(BrO_3)$ and HCl and the vapour condensed in an ice-cooled container [204]; from Ru(IV) or Ru(VI) species distilled with $K_2(S_2O_8)$ [205]; or from Cl_2 with aqueous $K_2[RuO_4]$ [203].

However, none of the oxidations described in this book requires the use of solid RuO_4. It is generated in solution, normally in a biphasic system from a lower oxidation state compound such as $RuO_2.nH_2O$ or $RuCl_3.nH_2O$[3], and a co-oxidant replenishes the RuO_4 reduced by the organic substrate (1.2.6).

[3] The hydrates $RuO_2.nH_2O$ or $RuCl_3.nH_2O$ are much more reactive than the anhydrous materials and are always used as such for oxidation catalysis. For brevity in this book, however, they will simply be referred to as RuO_2 and $RuCl_3$ respectively.

1.2.3 Physical Properties

These have been comprehensively reviewed: [6, 12, 17]. There is only one form of the solid [206] despite early claims that there were two. It is pale yellow and, like OsO_4, has a substantial vapour pressure at room temperatures; it melts at 25.4 ± 0.1°C [206], boiling at 129.6 ± 0.2°C [207]. Its density is 3.28 g/cm^3; the solubility in water at 0°C is 1.7% and 2.11% at 50°C, but it is very soluble in those organic solvents with which it does not react such as CCl_4 [6].

1.2.3.1 X-ray and Electron Diffraction Studies

The X-ray crystal structure of the solid shows that there are two crystal modifications, one cubic and one monoclinic, but within both forms the molecule is tetrahedral with Ru=(O) 1.695(3) Å [208]**.** Electron diffraction measurements on the vapour show the molecule to be tetrahedral with an Ru=(O) distance of 1.705(8) Å [209]. Similarity of the profiles of the Raman spectra of the solid, liquid and aqueous solution suggest that the molecule has tetrahedral symmetry in all three phases (Fig. 1.3) [210]. Aqueous solutions of RuO_4 are stable only at pH below 7 [211, 212].

1.2.3.2 Electronic and Vibrational Spectra

The electronic spectra of RuO_4, $[RuO_4]^-$ and $[RuO_4]^{2-}$ in aqueous solution of the appropriate pH are shown in Fig. 1.2 (in which the 385 and 320 nm. maxima are labelled I and II respectively) and the peaks listed in Table 1.1.

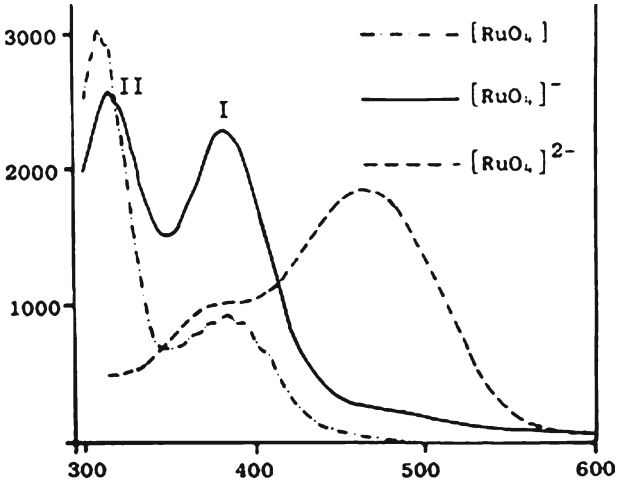

Fig. 1.2 Electronic spectra of RuO_4, $[RuO_4]^-$ and $[RuO_4]^{2-}$ in aqueous media [6] (Reproduced from the author and by Elsevier Ltd. With permission)

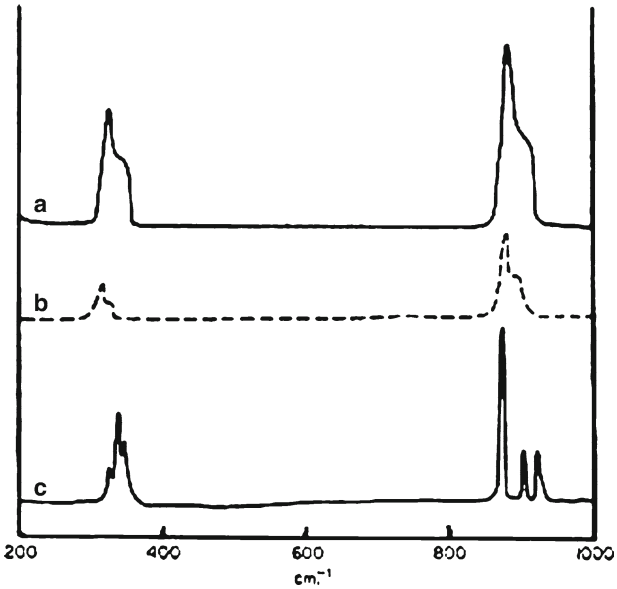

Fig. 1.3 Raman spectra of RuO_4 (**a**) pure liq.; (**b**) 5% aqueous soln.; (**c**) solid [210] (Reproduced from The Royal Society of Chemistry. With permission from [210])

Table 1.1 Electronic spectra[a] of RuO_4, $[RuO_4]^-$ and $[RuO_4]^{2-}$ in water [215]

RuO_4	310 (2960)[a]	385 (930)	–
$[RuO_4]^-$	310 (2445)	385 (2275)	460 (283)
$[RuO_4]^{2-}$	–	385 (1030)	460 (1820)

[a] λ in nm; ε in $dm^3M^{-1}cm^{-1}$

Table 1.2 Raman spectra[a] of RuO_4 (a) pure liquid; (b) 5% aqueous solution; (c) solid [210]

Fundamentals	$\nu_1(A_1)$	$\nu_2(E)$	$\nu_3(F_2)$	$\nu_4(F_2)$	Ref.
RuO_4					
Liquid	882[a]	323	914	334	[210]
Aq. soln.	883	318	921	332	[210]
Solid	881	324	922, 906	336,330	[210]
$[RuO_4]^-$					
K[RuO_4] solid	830	339	846	312	[226]
TPAP/CH_2Cl_2	844 (R^b)		843 (IR)	235 (IR)	[475]
$[RuO_4]^{2-}$					
$[RuO_4]^{2-}$/aq. KOH	807	291	828	291	[536]

[a] υ (cm^{-1})

[b] Polarised in Raman spectrum

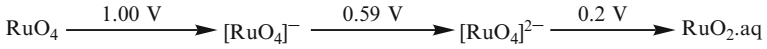

Fig. 1.4 Potential diagram for RuO_4-$[RuO_4]^-$-$[RuO_4]^{2-}$-RuO_2.aq [25, 227]

Other values of the wavelength λ and molar extinction coefficient ε have been given, e.g. in refs. [213] and [214] but differ little from the classic results of Connick and Hurley [215]. Such data can help in establishing which oxoruthenate species are present in oxidising solutions [212, 216]. A speciation diagram for RuO_4, $[RuO_4]^-$ and $[RuO_4]^{2-}$ based on electronic spectra has been given [217].

Raman spectra of RuO_4 in solid, liquid and aqueous solution phases were measured, all consistent with T_d symmetry for the molecule in these environments [210]; solid, liquid, vapour [218], solid, liquid [219], solid, liquid, vapour and for the normal and ^{18}O-substituted form of the liquid and vapour [220]. The Raman spectrum of the pure liquid (a) is very similar in profile to that of the aqueous solution (b) and of the solid (c), suggesting retention of tetrahedral symmetry in the solution (Fig. 1.3) [210]. As with electronic spectra, the Raman spectrum in particular can be useful for establishing the presence of RuO_4 in catalyst solutions [216, 221, 222].

IR spectra have been reported of isotopomers of RuO_4 with ^{16}O and ^{18}O in argon matrices [223]. Force-field calculations were made on the molecule [220, 224–226].

1.2.3.3 Electrochemical and Thermodynamic Data

The potential diagram for RuO_4 – $[RuO_4]^-$ – $[RuO_4]^{2-}$ – RuO_2.aq has been given [25], based on classic polarographic work of 1954 [227] (Fig. 1.4):

Other electrochemical data on RuO_4 have been obtained [228–230]. A Pourbaix (E-pH) diagram was given for RuO_4, $[Ru_4O_6]^{5+}$, $[Ru_4O_6]^{4+}$, $[RuO_4]^-$, RuO_2, Ru^{3+}, $Ru(OH)^{2+}$ and Ru^{2+} [231]. Thermodynamic data on RuO_4 and other Ru species were summarised [230, 232, 233], and reviewed [234]. Static electric dipole polarisabilities of RuO_4, OsO_4 and HsO_4 were calculated [235].

1.2.4 Analysis and Toxicity

The simplest method is probably colorimetric, based on its electronic spectrum [215]. It can also be determined gravimetrically by addition of diphenylsulfide or ethanol to a solution of RuO_4; this gives RuO_2 which is then reduced to the metal [236]. Alternatively addition of 2-propanol to a solution of RuO_4 solution generates $RuO_2.nH_2O$ [237].

Although it has been said [236] that RuO_4 is less harmful to the eyes than is OsO_4, nevertheless great care should always be taken in handling it. The high vapour pressure of the solid under ambient conditions makes it very dangerous

to the eyes and mucous membranes. It explodes above 100°C and can also explode when mixed with a variety of substances, e.g. HI, ethanol, diethylether, ammonia and a number of organic materials [238]. There are no oxidations in this book involving solid RuO_4, although frequent reference is made to its use in dilute solution. Nevertheless RuO_4 solutions, however weak, and indeed all Ru-containing materials, should be handled with care. Safety aspects of reactions involving RuO_4 generated from $RuCl_3$/TBHP/water-cyclohexane have been examined [186].

1.2.5 RuO_4 as an Organic Oxidant

As mentioned in 1.2.1 above, there are several reviews on the properties of RuO_4 as an oxidant in organic chemistry, both as a stoicheiometric but also as a catalytic reagent [12, 34–36, 39, 60, 64, 201–203]. It is one of the most important and versatile of Ru oxidants. In the first few years after its properties in the field were realised it was often used for oxidation of alcohol groups in carbohydrates, but its versatility as an oxidant quickly became apparent and its use was extended to a variety of other reactions, notably to alkene cleavage and, more recently, to the *cis*-dihydroxylation and ketohydroxylation of alkenes.

The properties of RuO_4 as an oxidant for organic substrates were first investigated by Djerassi and Engle in 1953 [236]. The use of OsO_4 as a selective oxidant had by then been recognised, both as a stoicheiometric and as a catalytic reagent, but RuO_4 is, by virtue of its position in the Periodic Table, a much fiercer oxidant. It was found that phenanthrene was converted to 9,10-phenanthrenequinone with a little 9,10-dihydrophenanthrene-9,10-diol, and a number of sulfides to mixtures of sulfoxides and sulfones [236]. In 1958 Berkowitz and Rylander carried out more systematic investigations using stoicheiometric RuO_4/H_2O, showing that it oxidised primary alcohols to aldehydes or carboxylic acids, aldehydes to acids, secondary alcohols to ketones, diols to the diones; alkenes were cleaved to acids and ethers to esters, amides to imides; benzene and pyridine were oxidised to intractable products [204]. The first use of RuO_4 as a catalyst seems to have been by Pappo and Becker, who in 1956 generated it *in situ* for oxidation of cholest-4-en-3-one (1) by the unusual mixture $RuO_2/Pb(OAc)_4$/aq. AcOH and also effected alkyne oxidation of 1,2-bis(1-acetoxycyclohexyl)ethyne (2) to a diketone: minimal experimental details were given. Fig. 1.5 shows two of the four oxidations accomplished by Pappo and Becker [239].

The publication used [239] is relatively obscure, and it was a paper of 1959 which really established the RuO_2/aq. $Na(IO_4)/CCl_4$ system[4] for production of RuO_4

[4] As indicated in 1.1 above, this takes the form: Ru starting material/co-oxidant/solvent; temperatures are only indicated if not ambient. For brevity RuO_2 and $RuCl_3$ denote the *hydrates* $RuO_2.nH_2O$ and $RuCl_3.nH_2O$.

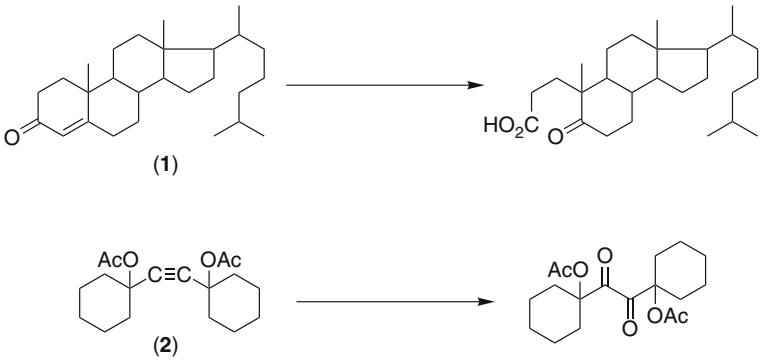

Fig. 1.5 The first catalytic oxidations by RuO_4 [239]

[240]. Although reference is often made (e.g. [241]) to Nakata's publication of 1963 as the standard procedure for this method, his use of it was more stoicheiometric than catalytic; however, Nakata was one of the first to use CCl_4 as a solvent for RuO_4 [237].

1.2.6 Co-oxidants and Solvents for RuO_4 Oxidations

Common procedures for making RuO_4 *in situ* generally use hydrated RuO_2 or $RuCl_3$ as starting materials. The dioxide RuO_2 is said to be preferable to $RuCl_3$ since oxidised chloro impurities are not formed and it may react faster than $RuCl_3$ [242]); hydrated rather than anhydrous RuO_2 should be used [243, 244].

1.2.6.1 Co-oxidants

Sodium periodate $Na(IO_4)$ (occasionally called sodium metaperiodate) is the commonest co-oxidant, e.g. as RuO_2/aq. $Na(IO_4)/CCl_4$ [240], RuO_2/aq. $Na(IO_4)$/EtOAc-CH_3CN [146], $RuCl_3$/aq. $Na(IO_4)/CCl_4$-CH_3CN [51]; *cf.* also 1.11. Very occasionally iodide from the reduced $(IO_4)^-$ can become incorporated into the organic reaction product (Fig. 3.21) [245]. Potassium periodate, as $RuCl_3$/aq. $K(IO_4)$/(BTEAC)/$CHCl_3$ is said to generate $[RuO_4]^-$ [246], but RuO_4 is probably the major product [213]. The low solubility of $K(IO_4)$ in water is disadvantageous, although it has been claimed that its use in oxidations of carbohydrates by RuO_4 renders over -oxidation less likely [247]. Periodic acid, $IO(OH)_5$, has long been known as a useful co-oxidant [248] and is becoming more popular, e.g. as in $RuCl_3$/aq. $IO(OH)_5/CCl_4$-CH_3CN [221, 249], or $RuCl_3$/aq. $IO(OH)_5/C_6H_{12}$ [216]; it is however a strong acid and this could affect some substrates. Bromate is an effective co-oxidant, e.g. $RuCl_3/Na(BrO_3)$/aq. HCl/CCl_4 [250], more so with ultrasound [242, 251]. Sodium bromate is much cheaper than $Na(IO_4)$, is equally efficient for