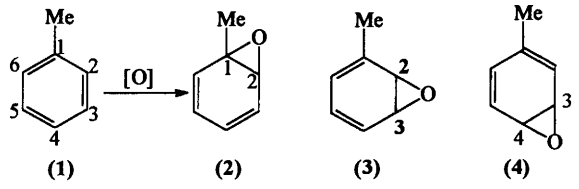
The Changing Face of Arene Oxide–Oxepine Chemistry

Derek R. Boyd* and Narain D. Sharma
School of Chemistry, The Queen's University of Belfast, Belfast, UK BT95AG

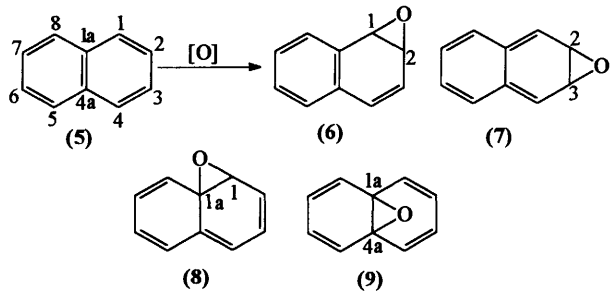
1 Introduction

The term 'arene oxide' is widely used to describe oxirane (epoxide) derivatives from chemical, *i.e.* non-enzyme-catalysed, and enzyme-catalysed epoxidation of mono- and poly-cyclic arenes. The increasing range of arene oxides reported in the literature, since the last major reviews of this topic appeared,[1,2] requires that the subject area be revised and updated. Particular emphasis will be placed upon advances in arene oxide chemistry which have appeared since 1983 and citations of earlier work will be covered by reference to the most recent review.[2]



Scheme 1 Possible arene oxide regioisomers from epoxidation of toluene **1**

Epoxides of toluene **1** and naphthalene **5** exemplify the range of possible monoarene oxide regioisomers in monocyclic and bicyclic arenes respectively. A simple epoxidation of such arenes would in principle yield three (**2**—**4**; Scheme 1) or four (**6**—**9**; Scheme 2) different oxirane regioisomers. In practice, however, due to aromatization and further epoxidation, only one of these seven arene oxides, *i.e.* oxide **6**, has been isolated from the direct chemical or enzyme-catalysed oxidation.[2] An additional factor is the preference for epoxidation of polycyclic arenes to occur at bonds of highest electron density and thus arene oxides **7**—**9** were not produced by this method.



Scheme 2 Possible arene oxide regioisomers from epoxidation of naphthalene **5**

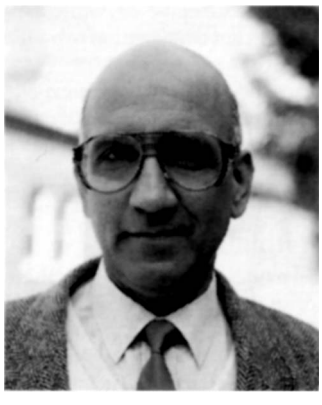
One type of arene oxide nomenclature, associated only with polycyclic members, is exemplified by reference to arene oxides of the pentacyclic arene benzo[*g*]chrysene **10** (Scheme 3). This is the simplest polycyclic aromatic hydrocarbon (PAH) containing **non-K**, **K-**, **bay-** and **fjord-** regions in the same molecule. In the literature,[2] the terms **non-K-region arene oxide** (*e.g.* **6**, **16**), **K-region arene oxide** (*e.g.* **15**), **bay-region arene oxide** (*e.g.* **12**—**14**) and **fjord-region arene oxide** (*e.g.* **11**, **17**), are used to identify epoxides proximate to these positions (bay and fjord region) or formed at the region of highest electron density (K-region) as shown in Scheme 3. Benzene oxides, *e.g.* of type **2**—**4**, are distinguished by reference to the approximate bond of the corresponding monosubstituted arenes, *e.g.* the arene 1,2-oxide **2** derived from toluene. Multiple epoxide derivatives of a PAH have been classified as **'polyarene oxides'** where the epoxides are in **different** arene rings, *e.g.* the 1,2,9,10-**diarene oxide** of benzo[*g*]chrysene **18**,[3] or as **'arene polyoxides'** where the epoxides are in the same arene ring, *e.g.* the 8,9,10,11-**arene dioxide** of benz[a]anthracene **19**.[4]

Fixed molecular geometry and configurational stability are normal characteristics of epoxide derivatives of cyclic alkenes. These static features are however less common in arene oxides where dynamic stereochemistry may result in spontaneous epoxide ring inversion between the faces of the arene *via* an oxepine (*e.g.* arene oxides **2**—**4** to the corresponding oxepines **20**—**22**) with concomitant racemisation at two chiral centres. Arene oxide derivatives of monocyclic arenes, *e.g.* benzene (**23**, R = H), toluene (**2**—**4**),

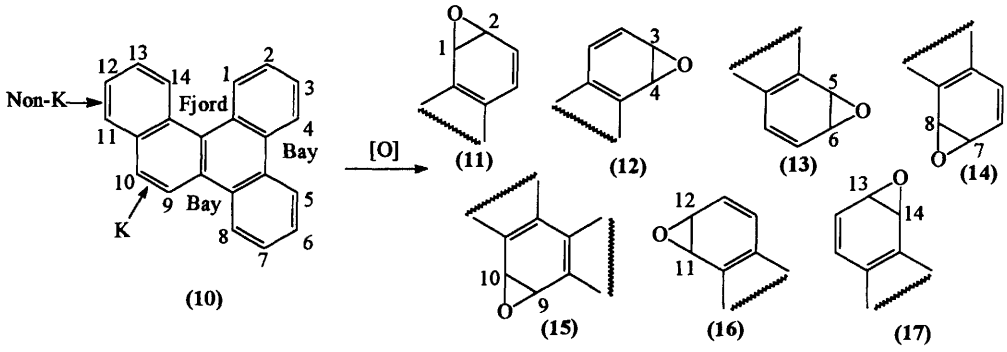
Derek Boyd has been involved in teaching and research at The Queen's University of Belfast for almost three decades. After graduating with a BSc (1963) and a PhD (1966) at Queen's he then joined the academic staff as a lecturer (1967).

Research interests in the chemical and enzyme-catalysed synthesis of chiral compounds followed from postgraduate and postdoctoral studies under the supervision of Professors H. B. Henbest and M. F. Grundon. This area of research was further stimulated by sabbatical leave spent at the National Institutes of Health, Bethesda, MD, in the laboratories with Drs. B. Witkop, J. Daly and D. M. Jerina (1968—69) and at the Massachusetts Institute of Technology, Cambridge, MA, in collaboration with Professor G. A. Berchtold (1977—78). The award of a Nuffield Foundation Science Research Fellowship and a NATO travel grant (with NIH and MIT) provided a further opportunity for full-time research and travel in the USA (1980—81).

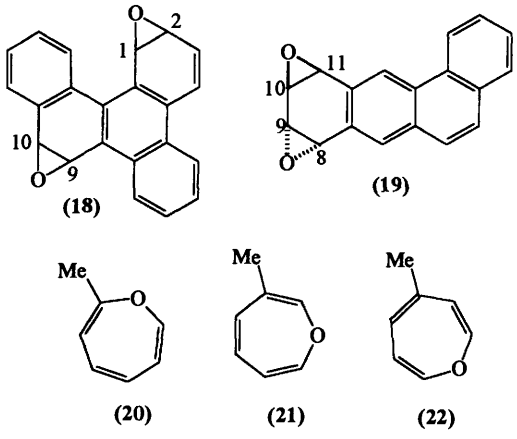
He was promoted to Reader (1978) and Professor of Organic Chemistry (1989) at Queen's where current research interests include chiral oxidations by chemical and enzyme-catalysed routes, applications of chiral bioproducts in synthesis, and the chemical and chemoenymatic synthesis of enantiopure alkaloids.



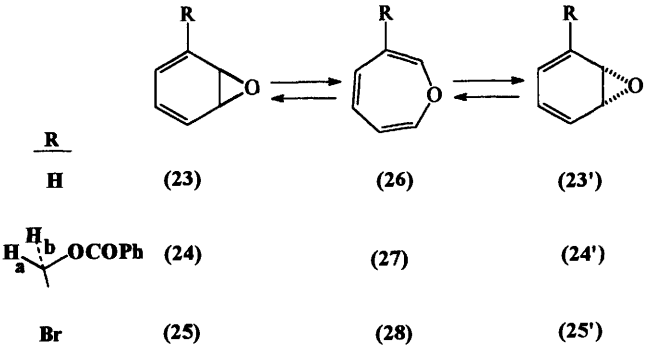
Narain Sharma was born in Simla, India in 1944. He obtained his MSc in 1967 from Kurukshetra University (Haryana, India) and a PhD from Delhi University in 1972. He served as a Lecturer and later as a Senior Lecturer in a Postgraduate College of Delhi University from 1972 to 1989. He is working as a Research Fellow in The Queen's University of Belfast.



Scheme 3 Possible arene oxides from epoxidation of benzo[*g*]chrysene **10**



benzyl benzoate (**24**), and bromobenzene (**25**) are generally assumed to exist in a state of rapid equilibration at ambient temperature with the corresponding valence tautomeric oxepines (**26**, **20**—**22**, **27** and **28**) *via* an electrocyclic rearrangement (Scheme 4).



Scheme 4 Arene oxide–oxepine equilibration

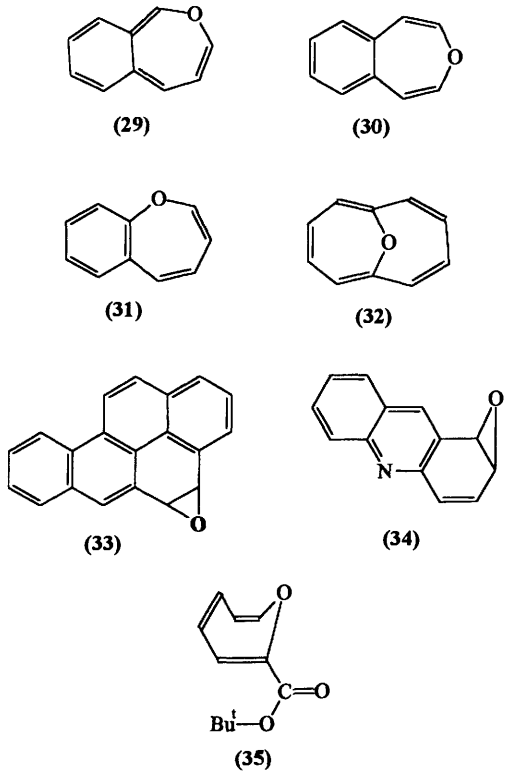
In contrast, the arene 1,2-oxide **6** of naphthalene showed no evidence of spontaneous isomerization to benzoxepine **29**, while oxepines **30**—**32** appeared to have no significant contribution from the tautomeric arene oxides **7**—**9**.

In the context of the changing shape and colour of benzene oxide (**23**, colourless), as it equilibrates with the seven-membered oxepine (**26**, bright yellow), this tautomeric system may be described as a 'molecular chameleon.'

2 Structure and Stereochemistry

The static stereochemistry of arene oxides, in both the cystalline state and in solution, has been demonstrated for the relatively stable K-region arene oxide series, by X-ray cystallography, and by the configurational stability of enantiomers, *e.g.* benzo[*a*]pyrene 4,5-oxide **33**.[2] K-region arene oxides are considered closer in structure, stereochemistry and reactivity to alkene epoxides.

Acridine 1,2-oxide **34**, a non-K-region arene oxide of sufficient



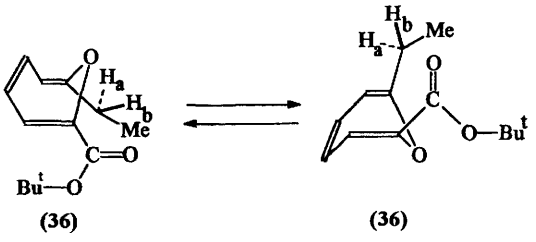
stability at room temperature to permit analysis by X-ray crystallography,[5,6] was also found to have fixed geometry with the epoxide ring at a similar external angle (*ca.* 80°) to the planar diene ring system and epoxide bonds of lengths similar to those of K-region arene oxides. The observed geometry of polycyclic arene oxides in the crystalline state was also predicted to be close to that for non-crystalline monocyclic arene oxides, *e.g.* benzene oxide **23**, based on molecular orbital calculations.[2] Evidence for the preferred oxepine tautomeric form (*e.g.* **20**) of arene 1,2-oxides of monosubstituted benzene oxides (*e.g.* **2**) is largely based on spectral data.[2] X-Ray crystallographic structure analysis of the relatively stable compound 1-*tert*-butoxycarbonyloxepine **35** confirmed unequivocally the predicted structure and the non-planar boat conformation.[7]

Arene oxide **34** was synthesised in enantiopure form and existed exclusively as a single valence tautomer in solution as well as in the crystalline state. Similarly oxepine **35** was the strongly preferred tautomer in solution and could be crystallized out exclusively. However, the parent arene oxide–oxepine system (benzene oxide–oxepine, **23** ⇌ **26**) was found to be in a finely balanced equilibrium in hydrocarbon solvents with the epoxide tautomer slightly favoured at lower temperatures and in hydroxylic solvents.[2] The enigmatic preference for an arene oxide or oxepine valence tautomer in the monosubstituted benzene series can now be predicted, from MINDO/3 calculations, and rationalized simply in terms of the maximum number of dipolar resonance structures which can be drawn.[2] Epoxides at the 2,3-bond of monosubstituted arenes bearing either a π-electron donating or withdrawing substituent will equilibrate rapidly showing a preference for arene 2,3-oxides (*e.g.*

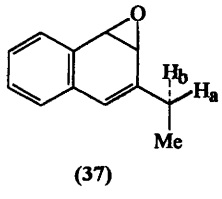
3) over oxepines (*e g* **21**) at ambient temperature Conversely arene 1,2 oxides (*e g* **2**) and arene 3,4-oxides (*e g* **4**), derived from the same arenes, will be very minor contributors to the equilibrum com pared with the corresponding oxepines (**20** and **22**)

Kinetic studies of arene oxide–oxepine valence isomerisation have been largely precluded by this marked substituent effect which causes the position of equilibrium to be heavily biased towards one particular valence tautomer Preference for the arene 2,3-oxide tautomer can, however, be helpful during dynamic NMR studies of enantiomerisation when a prochiral substituent is present For example, at −100 °C, in dimethyl ether solvent, the methylene protons H_a and H_b of arene oxide **24** are effectively enantiotopic and give a singlet signal due to rapid equilibration (*via* oxepine **27**) while at a lower temperatures (< −135 °C) the latter protons become diastereotopic and give an AB quartet (Scheme 4) This type of study has enabled the barrier to isomerization, of substituted benzene oxides to oxepines, to be measured ($\Delta G^{\ddagger}$ *ca* 7 6 kcal mol $^{-1}$, 1 cal = 4 184 J) [8] A more direct demonstration of the spontaneous enantiomerisation of monocyclic arene oxides, at ambient temperature, was provided when the arene 2,3-oxide of bromobenzene **25**, synthesised from the corresponding enantiopure 2,3-*cis*-dihydrodiol derivative of bromobenzene, was found to have totally racemised *via* the oxepine **28**[9] (Scheme 4)

Monocyclic oxepine tautomers, generally considered as achiral in solution due to rapid ring inversion, can account for the concomitant racemisation of two chiral centres in the corresponding arene oxides Molecular orbital calculations[2] have led to the conclusion that the barrier to inversion, of the boat conformation in the oxepine ring in solution, is very small ($\Delta G^{\ddagger}$ *ca* 0 7—1 2 kcal mol $^{-1}$) Using dynamic ^{1}H NMR spectroscopy, the barrier to ring inversion of the disubstituted oxepine **36** bearing a prochiral group (CH_aH_bMe) has been found[7] to be higher ($\Delta G^{\ddagger}$ *ca* 6 5 kcal mol^{-1}) (Scheme 5)



Scheme 5 Oxepine ring inversion



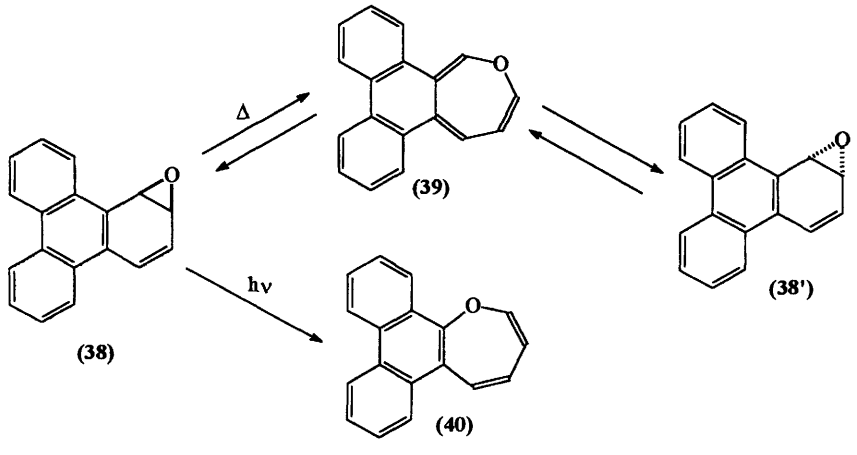
A similar attempt to measure the barrier to valence isomerisation and degenerate racemisation of the substituted naphthalene oxide **37**, by dynamic NMR methods, was unsuccessful due to (i) the much higher value ($\Delta G^{\ddagger}$ >> 23 kcal mol $^{-1}$) and (ii) compound instability above *ca* 100 °C [8] The high barrier to racemisation of naphthalene 1,2-oxide **6** is consistent with the relatively large loss in resonance energy involved in isomerisation to the corresponding oxepine **29** [2] A similar explanation in terms of resonance energies can be used to account for the exclusive preference for the oxepine tautomers **30**—**32** over the corresponding arene oxides **7**—**9** Perturbational molecular orbital (PMO) calculations have allowed the relative loss in resonance energy, associated with the tautomer isation of polycyclic arene oxides to the corresponding oxepines (and thus the configurational stability), to be predicted [2]

This approach led to the prediction and experimental verification that spontaneous racemisation, at ambient temperature, would only occur in particular arene oxides from members of the polycyclic aromatic hydrocarbon (PAH) series including phenanthrene, chrysene, triphenylene, benz[*a*]anthracene, benzo[*c*]phenanthrene, benzo[*e*]pyrene, dibenz[*a,h*]anthracene, dibenz[*a,j*]anthracene, dibenz[*a,c*]anthracene and benzo[*g*]chrysene [2] Configurational stability was predicted for other arene oxides of the latter PAHs including all K-region arene oxides and also for the non K- and bay region arene oxides of naphthalene, anthracene and benzo[*a*]-pyrene [2] A significant proportion of these predictions has been confirmed experimentally (*ca* 10 examples of spontaneously racemising arene oxides and *ca* 12 examples of configurationally stable arene oxides) and, to date, no exception to the rule has been found [2,10] Furthermore, it now appears that the results of PMO calculations can be extended to the prediction of ease of racemisation of azaarene oxides,[6] and should also be applicable to diarene oxides [11]

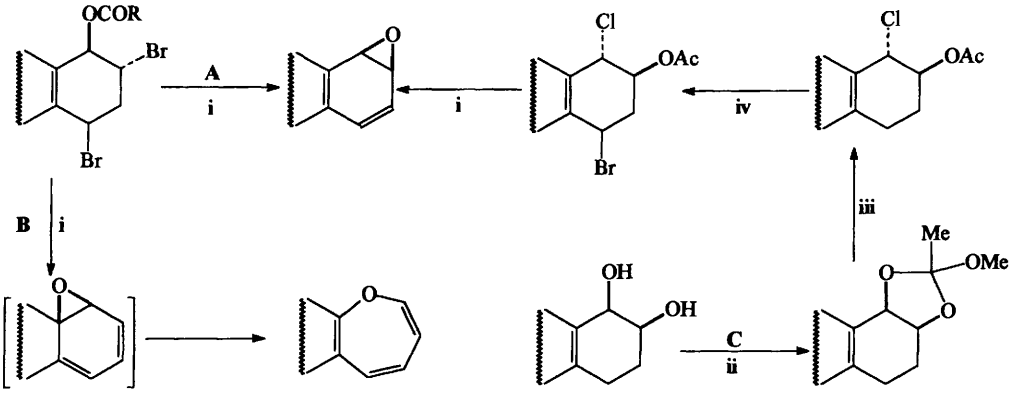
Where an arene oxide derivative from the PAH series, *e g* triphenylene 1,2-oxide **38**, is predicted[2] and found[12] to racemise spontaneously, *i e* $\Delta G^{\ddagger}$ < 23 kcal mol $^{-1}$, this may be accounted for by valence tautomerisation *via* a very minor proportion of the corresponding transient oxepine (*e g* **39**, Scheme 6) Direct evidence for the presence of this elusive valence tautomeric oxepine has not yet been obtained in any of the PAH systems studied

It is important to note that the undetected and less stable oxepine **39**, responsible for spontaneous epoxide ring inversion or racemisation of the arene oxide enantiomers of triphenylene 1,2-oxide **38**′ (*via* a disrotatory electrocyclic rearrangement mechanism), is structurally distinct from the more stable isomeric oxepine **40** The latter oxepine was of sufficient stability as to be isolated after photoisomerisation of arene oxide **38** (*via* a sigmatropic rearrangement mechanism) (Scheme 6) [12] Eight examples of relatively stable oxepines, structurally similar to compound **40**, have been found either as a result of a photochemically induced 'circumambulatory' ('oxygen walk') rearrangement of the arene oxide, or as a by-product formed during an attempted synthesis of the corresponding arene oxide from a dibromoester precursor (Scheme 7)

Formation of the more stable oxepines can also be predicted on



Scheme 6 Photoisomerisation of arene oxide **38** to a stable oxepine **40** and racemisation *via* an unstable oxepine **39**

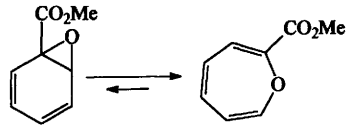


Scheme 7 *Reagents*: i, NaOMe; ii, $MeC(OMe)_3$; iii, Me_3SiCl–Et_3N; iv, *N*-bromosuccinimide (NBS)

the basis of the PMO calculations of resonance energy loss previously applied to rationalise the ease of racemisation of arene oxide enantiomers.[2,13]

3 Synthetic Methods

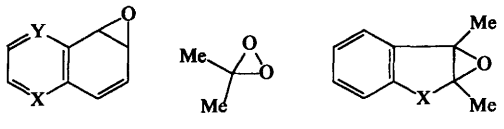
The recent availability of arene oxides by chemical (non-enzyme-catalysed) syntheses, and the resulting stability studies, have facilitated the first direct detection of monocyclic and polycyclic arene oxides in biological systems.



(41) (42)

The non-enzymatic synthesis, spectral characterisation and stability studies of methyl benzoate 1,2-oxide **41**,[2] which prefers to exist as the oxepine tautomer **42**, were instrumental in its subsequent identification as a secondary metabolite from the wood-rotting fungus *Phellinus tremulae*.[14] The synthesised quinoline 5,6-oxide **43**, and the isomeric arene 7,8-oxide **44**, were also remarkably stable. The stability of compound **43** allowed its isolation as a xenobiotic metabolite from monooxygenase-catalysed epoxidation of quinoline in the presence of an epoxide hydrolase inhibitor.[15]

Significant advances in the direct epoxidation of polycyclic arenes by chemical methods have been made by using dimethyldioxirane (DMD, **45**), a powerful neutral oxidant requiring a minimal workup procedure.[4,16–19] This method has been applied to the synthesis of relatively stable K-region monoarene oxides[4,16] and to the more labile arene oxide derivatives of five-membered aromatic heterocycles.[17–19] Thus substituted benzofuran and indole derivatives have been epoxidised at the 2,3-bond to yield the corresponding heterocyclic arene oxides, *e.g.* **46**[17,18] and **47**.[19,20] *N*-Acetylindole 2,3-oxide **47** is a crystalline solid while benzofuran 2,3-oxide **46** was only detected by ^1H NMR spectroscopy; it decomposed during attempted isolation.

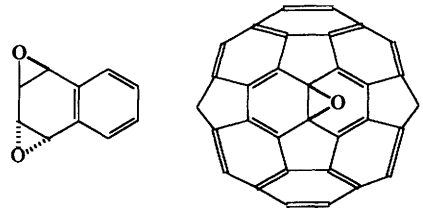


43 (X=N,Y=CH)
44 (X=CH,Y=N)

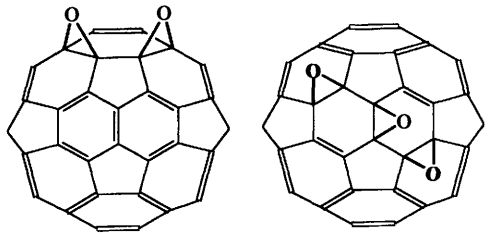
(45)

(46) X=O
(47) X=NCOMe

A problem associated with the direct epoxidation of PAHs, at non-K region positions, is the relatively slow rate of formation of monoarene oxides, *e.g.* **6**, compared with the much faster epoxidation of the alkene group of the arene oxide to yield diarene oxides, *e.g.* **48**.[4,16] As a result, direct non-enzymatic epoxidation does not generally provide a satisfactory route to non-K or bay-region monoarene oxides. The results of DMD oxidation of polycyclic arenes and heteroarenes have shown that, as expected, epoxidation occurs preferentially at the bond and ring having less aromatic and more alkene character. To date arene oxide derivatives, of aromatic heterocycles *e.g.* **46** and **47**, have only been obtained in racemic form and, therefore, their propensity to racemise or to retain configurational stability has not yet been examined.



(48) (49)



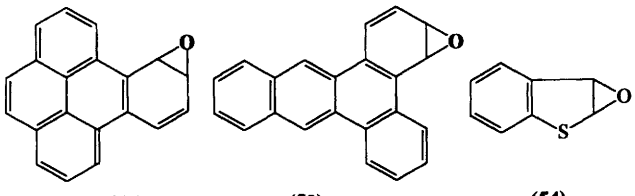
(50) (51)

The spherically symmetrical molecule C_{60} ([60]fullerene) contains an array of fused unsaturated five- and six-membered rings. The superficial similarity of C_{60} to strained and activated members of the PAH series has led to extensive studies of its direct epoxidation by a range of oxidants including DMD[21,22] and several model systems for monooxygenase enzymes (cytochrome P450).[23] Thus, epoxidation of one of the thirty equivalent double bonds of [60]fullerene yielded 1,2-epoxy [60]fullerene **49** without evidence of the corresponding oxepine tautomer which would have a structure similar to that of annulene **32**.[21] Sequential epoxidation of [60]fullerene, to yield the monoepoxide **49**, *cis*-diepoxide **50** and *cis*, *cis*-triepoxide **51**, has been reported using the tetraphenylporphyrinatoiron(III) chloride-iodosylbenzene P450 chemical model system.[23] Although compounds **49**—**51** have some features similar to those of arene oxides in the PAH series, *e.g.* **9**, **18** and **19**, the reactivity of C_{60} is closer to that of an arene K-region or an alkene. Multiple site epoxidation of C_{60} can only occur on the outer surface to yield *cis*-products, *e.g.* di- and tri-epoxy[60]fullerenes **50** and **51** respectively. This contrasts with the epoxidation of planar PAHs where epoxides are formed on either face to yield *trans*-arene dioxides, *e.g.* **19**.

The most widely used synthesis of PAH oxides involves the treatment of dibromoesters with base.[2] Arene oxides **6**,[2] **34**,[5] **43**[15] and **44**[15] were obtained in good yields and in enantiopure form using this method (Scheme 7, route A). Arene oxides **13**,[3] and **14**[3] and

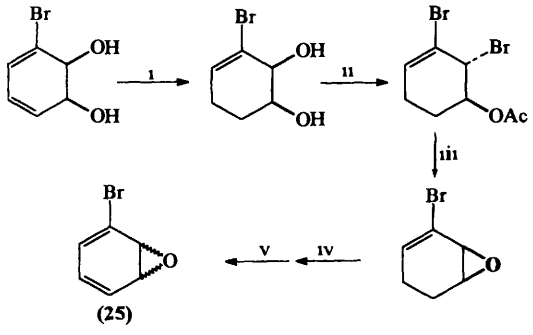
38[12] were accompanied by the corresponding stable oxepine tautomers, *e g* **40**, formed by competitive S_N2' displacement (Scheme 7, route B)

An alternative synthetic approach is based on the conversion of *cis*-diol precursors *via* dioxolane and chloroacetate intermediates, and offers significant advantages including allowing the arene oxide tautomer, *e g* triphenylene 1,2-oxide **38**, to be obtained exclusively (Scheme 7, route C) [24] The availability of enantiopure *cis*-dihydrodiol metabolites of monocyclic and bicyclic arenes (*e g* bromobenzene, naphthalene and quinoline), from dioxygenase-catalysed oxidation using mutant strains of the soil bacterium *Pseudomonas putida*, and their regioselective catalytic hydrogenation to the corresponding *cis*-tetrahydrodiol enantiomers, has also facilitated the synthesis of arene oxide enantiomers Thus, naphthalene, 1,2-oxide **6**, quinoline 5,6-oxide **43**, and quinoline 7,8-oxide **44** were all obtained in enantiopure form from the corresponding *cis*-dihydrodiol precursors [24] The synthetic method (Scheme 7, route C) provides a valuable link between the two major metabolic pathways for aromatic rings in nature Thus, the readily available initial metabolites of arenes (*cis*-dihydrodiols) in procaryotic systems (bacteria) can, in turn, become chiral precursors for the non-enzymatic synthesis of the elusive initial arene metabolites (arene oxides) in eucaryotic systems (plants, animals, and fungi)



(52) (53) (54)

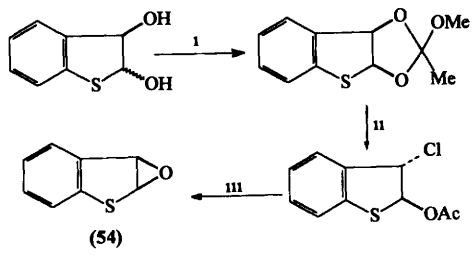
Racemic samples of arene oxides **38**, **52** and **53** derived from triphenylene, benzo[*e*]pyrene and dibenz[*a*,*c*]anthracene respectively (previously unavailable without contamination by the corresponding oxepine isomers of structure similar to that of compound **40**) were obtained in pure form from the appropriate *cis*-tetrahydrodiol precursors [24] The synthesis of racemic arene 2,3-oxides of monosubstituted benzenes, *e g* bromobenzene 2,3-oxide **25** from *cis*-2,3-dihydroxy-2,3-dihydrobromobenzene, has also been achieved by this approach[9] (Scheme 8)



Scheme 8 *Reagents* i, H_2 Rh, Al_2O_3, ii, $AcOCMe_2COBr$, iii, NaOMe, iv, NBS, v, DBU

Preliminary studies[25] have shown that the *cis*-dihydrodiol methods used in Schemes 7 and 8 are also applicable to the synthesis of 3,4-arene oxides of monosubstituted benzenes and to arene oxides of aromatic heterocycles For example, the *cis*-2,3-diol metabolite of benzothiophene can also be converted *via* the dioxolane–chloroacetate route to the corresponding benzothiophene 2,3-oxide **54** (Scheme 9) [25]

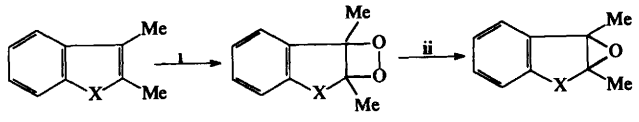
The labile compound **54** was only detected in solution by ^1H NMR spectroscopy Since arene 2,3-oxides of benzothiophenes have not yet been synthesised *via* the direct (DMD) oxidation route[17–20] used for arene 2,3-oxides of the corresponding benzofuran **46** and indole **47**, the *cis*-diol route (Scheme 9) may therefore be complementary



(54)

Scheme 9 *Reagents* i, $MeC(OMe)_3$, ii, Me_3SiCl–Et_3N, iii, NaOMe

The arene 2,3-oxides **46** and **47** have also been synthesised by photosensitized oxygenation of the corresponding benzofuran and indole precursors using singlet oxygen to yield the 2,3-dioxetanes **55** and **56** followed by partial deoxygenation using dimethyl sulfide[17 19] (Scheme 10)



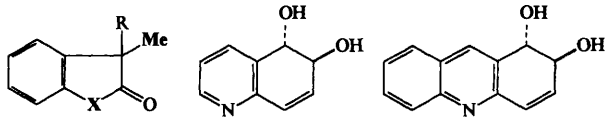
X=O, X=NCOMe (55) (56) (46) (47)

Scheme 10 *Reagents* i, O_2, ii, Me_2S

4 Non-enzymatic and Enzymatic Reactions of Arene Oxides

Amongst the more widely studied reactions of arene oxides are (*i*) isomerisation to yield oxepines, ketones and phenolic products, (*ii*) ring opening with nucleophiles and (*iii*) oxidation–reduction processes [2] Arene oxides are commonly found as mammalian metabolites of carbocyclic and heterocyclic arenes and, in this context, transformations (*i*)—(*iii*) are of considerable interest since their products may be linked to particular biological activity, *e g* cytotoxicity, mutagenicity and carcinogenicity of arenes [2] The development of new synthetic routes to arene oxides from heterocyclic arenes,[17–20 24] and larger PAHs,[23] has also extended the range of possibilities for enzyme-catalysed studies

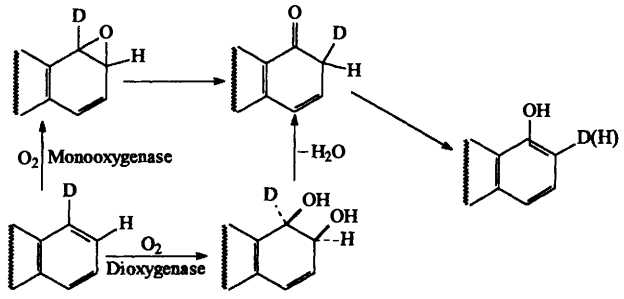
Spontaneous interconversion of arene oxide–oxepine tautomers has been observed in monocyclic and PAH systems (Section 2) Thus the oxepine tautomers, **20** and **21**, of substituted 1,2- and 3,4-benzene oxides are generally preferred, whereas substituted benzene 2,3-oxides, *e g* **3**, and most PAH arene oxides, *e g* **6**, **11**—**17** and **38**, exist almost exclusively in the arene oxide form (Schemes 1—3 and 6) Synthesis and spontaneous racemisation of the arene oxide **38** of triphenylene is consistent with equilibration *via* the undetected oxepine **39** The stable oxepine **40** was, however, formed upon exposure of arene oxide **38** to sunlight This facile photoisomerisation process has only been observed among arene oxides in the tetracyclic and larger members of the PAH series [13]



X=O,R=Ph (57) X=NCOMe,R=Me (58) (59) (60)

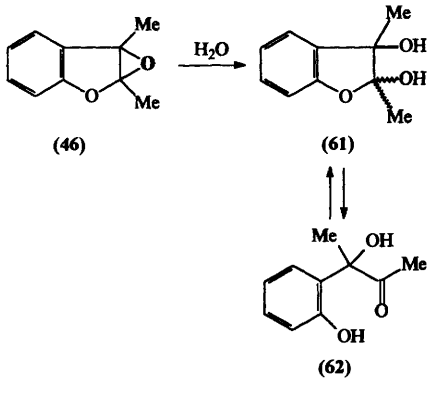
Isomerisation of arene 2,3-oxides in the benzofuran and indole series has been reported to yield a series of products containing a carbonyl group Products isolated include lactone **57**[18] and lactam **58**[20] which involve migration of a methyl group from the C-2 to the C-3 position The migration of an atom (*e g* D or Cl) or a group (*e g* Me or CO_2Me) from one carbon atom and retention on an adjacent carbon during the enzyme-catalysed hydroxylation of an arene has been described as the 'NIH shift' (after its discovery at the National Institutes of Health, Bethesda, USA) (Scheme 11) To date more than 100 examples of the 'NIH shift' have been

reported.[2] This phenomenon has become widely associated with the monooxygenase-catalysed formation of arene oxides and their *in situ* isomerisation to ketodienes. Compounds **57** and **58** parallel the ketodiene products associated with the 'NIH shift.' The thermal or acid-catalysed isomerisation of specifically labelled samples of 1- and 2-deuterio-naphthalene oxides (**6**) and 5-, 6-, 7- and 8-deuterio-quinoline oxides (**43**, **44**) to the corresponding phenols showed typical 'NIH shift' behaviour.[26] Recent evidence[26] suggests that the assumption of a link between arene oxide metabolites and the occurrence of the 'NIH shift' during enzyme-catalysed aromatic hydroxylation may not be correct in all cases, particularly in the context of bacterial hydroxylations. An alternative explanation for the 'NIH shift' has been provided by results obtained from bacterial hydroxylation of arenes and heteroarenes, where the phenolic metabolites have been obtained from the dioxygenase-catalysed oxidation of arenes to yield unstable *cis*-dihydrodiol metabolites which can readily dehydrate. Phenols resulting from dehydration of *cis*- and *trans*-dihydrodiols or from the isomerisation of arene oxides all showed similar evidence of the migration and retention of label, *i.e.* the 'NIH shift' (Scheme 11).



Scheme 11 Aromatic hydroxylation and the 'NIH shift'

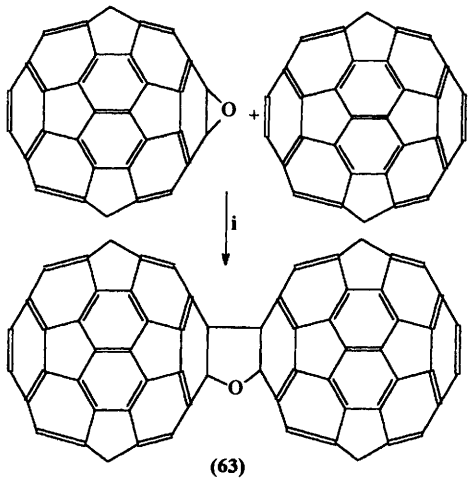
Hydrolysis of mono-and poly-cyclic arene oxides to form *trans*-dihydrodiols is catalysed by epoxide hydrolase enzyme systems but, with the exception of K-region arene oxides, until relatively recently this could not be achieved by non-enzymatic methods.[2] The observation[5,27] that *trans*-dihydrodiols **59** and **60** can be obtained by non-enzymatic hydrolysis of the corresponding stable non-K arene oxides of the aromatic heterocycles quinoline **43** and acridine **34** under a range of pH conditions is hence unusual. Arene oxide derivatives of the heterocyclic ring of benzofuran, *e.g.* **46**, proved to be even more reactive and readily hydrolysed to an equilibrating mixture of *cis*- and *trans*-diols **61** and the isomeric acyclic ketones **62**[17] (Scheme 12).



Scheme 12 Hydrolysis of benzofuran 2,3-oxide **46**

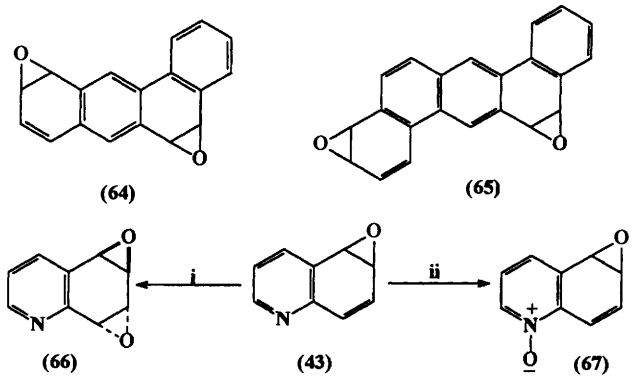
Confirmation that 1,2-epoxy[60]fullerene **49** should be treated as an 'abnormal' arene oxide is provided by the unprecedented observation that it undergoes a thermal cycloaddition with [60]fullerene to give the novel structure **63** (Scheme 13).[28]

Epoxidation of arene oxides with the neutral oxidizing agent DMD **45** occurs either in the same ring, *e.g.* to form arene dioxides **19** and **48**, or in a more remote ring containing a K-region, *e.g.* to



Scheme 13 *Conditions*: i, Heat (solid mixture), 6 h

yield diarene oxides **64** and **65**.[4,16] Evidence of enzyme-catalysed arene oxide formation as the initial step in the 'bay-region diol-epoxide pathway' for the mammalian metabolism of PAHs is now widely accepted.[2] Reports[4,11] suggest that the initial arene oxide metabolites may also undergo monooxygenase-catalysed epoxidation to yield both arene dioxide, *e.g.* **48**,[11] and diarene oxide, *e.g.* **65**,[29] metabolites.

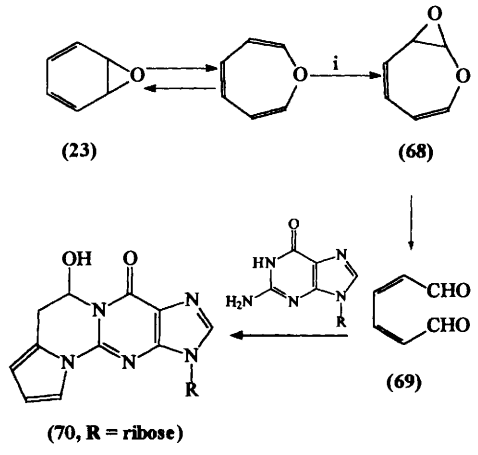


Scheme 14 *Reagents*: i, MCPBA; ii, NaOCl

The 'bay-region diol-epoxide pathway' for the mammalian metabolism of PAHs involves the metabolic sequence: arene → arene oxide → *trans*-dihydrodiol → *vicinal* diol epoxide, occurring in one arene ring proximate to a bay-region.[2] This bioactivation route has been confirmed for many members of the PAH series including the procarcinogens benzo[*a*]pyrene, benz[*a*]anthracene and benzo[*c*]phenanthrene. Recent reports,[11,30] however, have suggested that alternative metabolic pathways may involve the initial formation of an arene oxide followed by further epoxidation in a different ring of the PAH. Mammalian metabolism of the PAHs chrysene, benzo[*a*]pyrene, dibenz[*a*,*h*]anthracene and cyclopenta[*c*,*d*]pyrene thus appear to involve two independent epoxidation steps during the formation of the corresponding bis-arene oxide, *trans*-dihydrodiol monoarene oxide, phenol monoarene oxide, phenol *trans*-dihydrodiol, and bis-*trans*-dihydrodiol products.[11,30]

Non-enzymatic oxidation of polycyclic azaarene oxides may result in competition between epoxidation or heteroatom oxidation, to yield either an arene dioxide or an *N*-oxide arene oxide, according to the choice of oxidant. Use of a peroxyacid resulted in epoxidation of the arene oxides **43** within the same ring to yield the *trans*-diarene oxide **66**, while oxidation using NaOCl gave the *N*-oxide **67**[31] (Scheme 14). Although the epoxidation of arene oxide derivatives of PAHs is a relatively fast reaction, the epoxidation of monocyclic arene oxides–oxepines is much slower and attempts to isolate arene dioxides, arene trioxides, or oxepine epoxides have

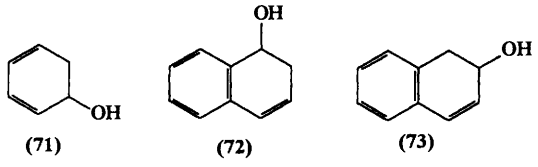
generally been unsuccessful [2] Peroxyacid epoxidation of benzene oxide–oxepine has been assumed to proceed by oxidation of the vinyl ether bond to yield an unstable oxepine epoxide **68** which readily opened up to yield the isomeric *Z,Z*-mucondialdehyde **69** [2]



Scheme 15 *Reagent* i, $PhCO_3H$

The reaction of mucondialdehyde isomers with cellular amines to yield cyclic adducts, *e g* compound **70** from reaction with guanosine, is of interest in the context of the carcinogenicity of benzene[32,33] (Scheme 15)

It has been postulated that nucleophilic attack resulting in opening of the epoxide ring in the labile oxides **68** and **46**, occurring *in vivo*, is an important step in the formation of DNA adducts, it may also contribute to the mutagenicity/carcinogenicity of benzene and furan derivatives [32–34]



The reduction of benzene oxide using $LiAlH_4$ provides a convenient route to the racemic benzene hydrate **71** [2] This method has been extended to the synthesis of enantiopure arene hydrates of PAHs, several (*e g* **72**, **73**) of which have been reported as metabolites of dihydroarenes [35] To date, however, no evidence for the enzyme-catalysed reduction of arene oxide metabolites, to yield arene hydrates, has been reported Studies on the relative rates of aromatisation of arene oxides (phenol formation) and arene hydrates (dehydration) have shown that arene oxides appear to have an unexpected additional stability due to homoaromaticity [36] This enhanced stability of arene oxides is relevant to their formation and reactivity in biological systems

5 Summary

Alternative and improved methods of synthesis have recently opened up new possibilities in arene oxide chemistry The synthesis of oxide derivatives of heterocyclic arenes both in the carbocyclic (quinoline, isoquinoline, acridine) and heterocyclic rings (indole, thiophene, furan), which had previously only been postulated as transient intermediates in metabolism, has finally been realised in the laboratory Some of these advances have only been possible with the development of powerful new oxidants such as dimethyldioxirane (which can effect direct oxidation of arenes under mild neutral conditions) Epoxide derivatives of [60]fullerene can also be produced by direct oxidation and these, in turn, provide entry into a new range of structures including linked C_{60} units The availability of *cis*-dihydrodiol derivatives as chiral synthons from bacterial metabolism of mono- and poly-cyclic arenes has also provided a simple new approach to the synthesis of arene oxides

The role of arene oxides in biological systems continues to attract attention The earlier focus upon two separate epoxidation steps, occurring within one PAH bay-region ring to yield diol epoxides, has been successfully linked to the mutagenic–carcinogenic properties of PAHs Attention has also recently moved toward consideration of the biological consequences of monoepoxidation in two different arene rings and their derivatives While some progress has already been made in the synthesis of diarene oxides, further studies are required to develop regioselective routes to the putative phenol–arene oxide, and *trans*-dihydrodiol–arene oxide types of metabolites and to examine their biological properties Based upon current understanding of the molecular basis for haemotoxicity in benzene, it is anticipated that the enzyme-catalysed epoxidation of monocyclic arenes, to yield oxepines and their transient epoxide derivatives, will receive further attention The development of synthetic routes to the elusive oxepine epoxides would greatly facilitate such studies

Enzyme-catalysed synthesis of arene oxides has arguably been in progress since the origin of life itself Despite their origins in remote antiquity, studies of the structure, chemistry, and biochemistry of these generally unstable compounds have only been carried out over the past thirty years The face of these chameleon-like molecules will undoubtedly continue to change and attract attention from both chemists and biologists well into the new millenium

Acknowledgements We gratefully acknowledge financial support from the BBSRC (to N D S)

6 References

1 G S Shirwaiker and M V Bhatt, *Adv Heterocycl Chem* , 1984, **37**, 67
2 D R Boyd and D M Jerina, in *Small Ring Heterocycles, Part III*, in *The Chemistry of Heterocyclic Compounds*, ed A Hassner, Interscience, New York, 1985, vol 45, p 197, and references therein
3 S K Agarwal, D R Boyd and W B Jennings, *J Chem Soc , Perkin Trans 1*, 1985, 857
4 S K Agarwal, D R Boyd, W B Jennings, R M McGuckin and G A O'Kane, *Tetrahedron Lett* , 1989, **30**, 123
5 D R Boyd, R J H Davies, L Hamilton, J J McCullough, J F Malone, H P Porter, A Smith, J M Carl, J M Sayer and D M Jerina, *J Org Chem* , 1994, **59**, 984
6 D R Boyd, M R Dorrity, L Hamilton, J F Malone and A Smith, *J Chem Soc , Perkin Trans 1*, 1994, 2711
7 W B Jennings, M Rutherford, S K Agarwal, D R Boyd, J F Malone and D A Kennedy, *J Chem Soc , Chem , Commun* , 1986, 970
8 W B Jennings, M Rutherford, D R Boyd, S K Agarwal and N D Sharma, *Tetrahedron*, 1988, **44**, 7551
9 D R Boyd, N D Sharma, H Dalton and D A Clarke, *J Chem Soc , Chem Commun* , 1996, 45
10 D R Boyd, N D Sharma, S K Agarwal, G S Gadaginamath, G A O'Kane, W B Jennings, H Yagi and D M Jerina, *J Chem Soc , Perkin Trans 1*, 1993, 423
11 S K Agarwal, D R Boyd, M R McGuckin, W B Jennings and O W Howarth, *J Chem Soc , Perkin Trans 1*, 1990, 3073
12 D R Boyd, D A Kennedy, J F Malone, G A O'Kane, D R Thakker, H Yagi and D M Jerina, *J Chem Soc , Perkin Trans 1*, 1987, 369
13 S K Agarwal and D R Boyd, *J Chem Soc , Perkin Trans 1*, 1993, 2869
14 W A Ayer and E R Cruz, *Tetrahedron Lett* , 1993, **34**, 1589
15 S K Agarwal, D R Boyd, H P Porter, W B Jennings, S J Grossman and D M Jerina, *Tetrahedron Lett* 1986, **27**, 4253
16 R Jeyaraman and R W Murray, *J Am Chem Soc* , 1984, **106**, 2462
17 W Adam, L Hadjiarapoglou, T Mosandl, C R Saha Moller and D Wild, *J Am Chem Soc* , 1991, **113**, 8005
18 W Adam, L Hadjiarapoglou, K Peters and M Sauter, *Angew Chem , Int Ed Engl* , 1993, **32**, 735
19 W Adam, M Ahrweiler, M Sauter and B Schmiedeskamp, *Tetrahedron Lett* , 1993, **34**, 5247
20 X Zhang and C S Foote, *J Am Chem Soc* , 1993, **115**, 8867
21 Y Elemes, S K Silverman, C Sheu, M Kao, C S Foote, M M Alvarez and R L Whetton, *Angew Chem , Int Ed Engl* , 1992, **31**, 351

22 A L Balch, D A Costa, B C Noll and M M Olmstead, *J Am Chem Soc*, 1995, **117**, 8926
23 T Hamano, T Mashino and M Hirobe, *J Chem Soc, Chem, Commun*, 1995, 1537
24 D R Boyd, N D Sharma, R Agarwal, N A Kerley, R A S McMordie, A Smith, H Dalton, A J Blacker and G N Sheldrake, *J Chem Soc, Chem Commun*, 1994, 1693
25 D R Boyd, S A Haughey and N D Sharma, unpublished data
26 S A Barr, D R Boyd, N D Sharma, L Hamilton, R A S McMordie and H Dalton, *J Chem Soc, Chem Commun*, 1994, 1921
27 D R Bushman, J M Sayer, D R Boyd and D M Jerina, *J Am Chem Soc*, 1988, **111**, 2688
28 S Lebedkin, S Ballenweg, J Gross, R Taylor and W Kratschmer, *Tetrahedron Lett*, 1995, **36**, 4971
29 K L Platt and I Reischmann, *Mol Pharm*, 1987, **32**, 710
30 D H Phillips and P L Grover, *Drug Metabolism Rev*, 1994, **26**, 443
31 D R Boyd, R J H Davies, L Hamilton, J J McCullough and H P Porter, *J Chem Soc, Perkin Trans 1*, 1991, 2189
32 C Bleasdale, B T Golding, G Kennedy, J O MacGregor and W P Watson, *Chem Res Toxicol*, 1993, **6**, 407
33 W P Watson, C Bleasdale and B T Golding, *Chem Br*, 1994, **30**, 661
34 W Adam, M Ahrweiler, D Reinhardt and M Sauter, *Tetrahedron Lett*, 1994, 6063
35 R Agarwal, D R Boyd, R A S McMordie, G A O'Kane, P Porter, N D Sharma, H Dalton and D J Gray, *J Chem Soc, Chem Commun*, 1990, 1711
36 S N Rao, R A More O'Ferrall, S C Kelly, D R Boyd and R Agarwal, *J Am Chem Soc*, 1993, **115**, 5458