Oxyfunctionalization of Benzofurans by Singlet Oxygen, Dioxiranes, and Peracids: Chemical Model Studies for the DNA-Damaging Activity of Benzofuran Dioxetanes (Oxidation) and Epoxides (Alkylation)‡

MARKUS SAUTER AND WALDEMAR ADAM*

Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, FRG

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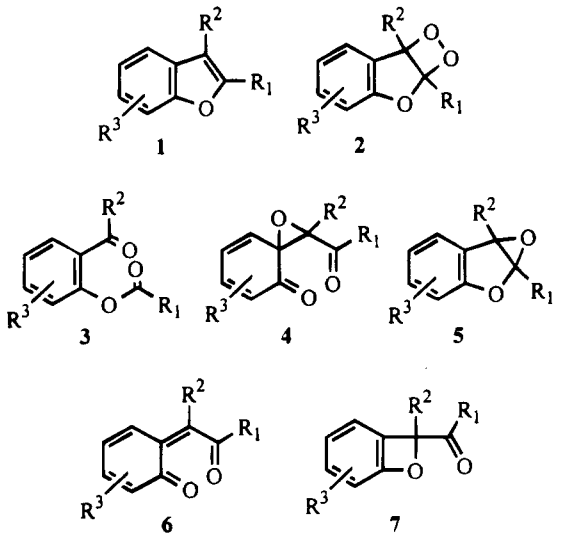
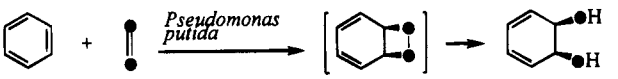
The present Account covers the chemistry of oxyfunctionalized benzofuran **1** derivatives. It includes, on the one hand, the photooxygenation to the dioxetanes **2** and the fragmentation of the latter to the keto esters **3** or rearrangement to the spiroepoxides **4**. On the other hand, the dioxirane oxidation to the epoxides **5** and their valence-isomeric quinone methides **6** and benzoxetes **7** are described. The chemistry of the dioxetanes **2** and epoxides **5** and their relevance in genotoxicity are presented.



Introduction

There exists cogent evidence that the high-energy and reactive 1,2-dioxetanes are involved as labile intermediates in the dioxygenase-activated aerobic metabolism in cellular processes. In particular, arenes such as benzene[1] and naphthalene[2,3] and heteroarenes such as benzofuran[4] are aerobically metabolized by the microorganism *Pseudomonas putida* to the corresponding *cis*-diols, a process which presumably proceeds through dioxetane intermediates. In the case of benzene,[1] it was demonstrated by ^{18}O-labeling

Scheme 1



experiments that a dioxetane is a plausible intermediate in this microbial oxidation[1] (Scheme 1), since both incorporated oxygen atoms derive from the same dioxygen molecule. Besides, the *cis*-configuration of the *vicinal* diol excludes the popular[5] arene oxide mechanism as a possible alternative.

Indeed, extensive investigation on the genotoxicity of 1,2-dioxetanes has shown that they induce a variety of DNA lesions.[6] Thus, in cell-free calf thymus DNA, 3,3,4-trimethyl-1,2-dioxetane leads to pyrimidine dimers.[7,8] On the other hand, in supercoiled DNA of the bacteriophage PM2, the alkyl-substituted dioxetanes induce predominantly endonuclease-sensitive base modifications but relatively few single-strand breaks and little base loss (AP sites).[6,9] However, only a small fraction of the base modifications consist of pyrimidine dimers, as established by employing a specific UV endonuclease preparation from *Micrococcus luteus*.[9]

Contrary to the above-mentioned alkyl-substituted dioxetanes, heteroarene derivatives such as the benzofuran dioxetanes **2** are the first known cases with strong mutagenic activity in the *Salmonella typhimurium* strain TA100.[10a] Similar mutagenicity was noted for the furocoumarin-derived dioxetanes.[10b] The mu-

Markus Sauter, born in Germany, commenced his chemistry studies in 1985 at the University of Würzburg and joined Prof. Adam's research group in 1990 (Diplom 1991, Dr. rer. nat. 1994). He has coauthored 18 publications during his graduate work, which form the basis of this Account.

Waldemar Adam, born in the Ukraine, raised in Germany, educated in the United States (B.Sc. 1958, University of Illinois; Ph.D. 1961, MIT with F. D. Greene), started his academic career in 1969 at the University of Puerto Rico (Rio Riedras), where he was promoted to full professor in 1970. Postdoctoral work with R. Criegee (1962, Karlsruhe) kindled his interest in valence isomerizations, which he has pursued to this day. In 1980 he was appointed to the Chair of Organic Chemistry at the University of Würzburg. He has lectured in over 60 countries of the five continents, has received numerous prizes, and is coauthor of well over 500 scientific publications.

‡ We dedicate this article to Prof. G. Modena (Padova) on the occasion of his 70th birthday in admiration of his pioneering work in oxidation chemistry!

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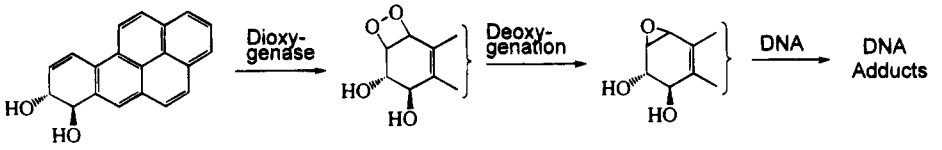
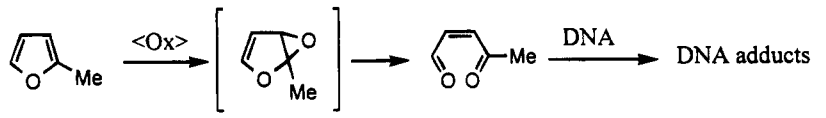
Scheme 2



Scheme 3



tagenic DNA lesions caused by the benzofuran dioxetanes **2** are not derived from pyrimidine dimers, but are rather due to the DNA adducts formed from an intermediary alkylating agent. The latter has been postulated to be generated *in situ* by dioxetane deoxygenation. In view of the fact that benzofuran dioxetanes **2** can be quantitatively deoxygenated *in situ* to the corresponding benzofuran epoxides **5** by sulfides, e.g., L-methionine, such epoxides have been proposed as the ultimate mutagens in the DNA damage. Support for this hypothesis rests on the fact that the benzofuran epoxides **5** are also strong mutagens in the *S. typhimurium* strain TA100 and that they form DNA adducts, as detected by the ^{32}P-postlabeling technique.[10a] Since dioxetanes are potential cellular intermediates, which are produced in the oxidative metabolism of arenes and olefins, their deoxygenation to the highly reactive epoxides as ultimate mutagen, as illustrated for benzopyrene in Scheme 2, may comprise a new mutagenic mechanism of general scope.[10a] Furthermore, it has been postulated that heteroarene epoxides, for instance furan epoxides (no persistent derivative has been observed as yet), are responsible for the observed cytotoxicity in their oxidative metabolic activation by cytochrome P 450.[10c] Indeed, the valence-isomeric *cis*-enediones of the furan epoxides efficiently afforded DNA adducts due to their strongly electrophilic nature (Scheme 3).[10d]

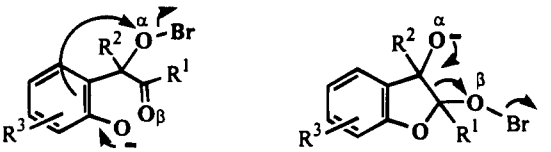
In this context, it was relevant to prepare authentic benzofuran epoxides **5**, examine the chemistry of these transient species, particularly their electrophilic reactivity (alkylation), and compare their chemical behavior with that of the corresponding 1,2-dioxetanes **2** (Scheme 4). Such information would provide the necessary chemical model studies to understand the oxidative and alkylative damage of DNA promoted by benzofuran dioxetanes **2** and the corresponding epoxides **5**.

Benzofuran Dioxetanes 2

Synthesis. The benzofuran dioxetanes[11] **2**, first reported by Wasserman,[11a] can be readily obtained by the TPP-sensitized photooxygenation (Scheme 5) of benzofurans **1**. Analogously the related furocoumarin dioxetanes[10b] are prepared from the respective furocoumarins as precursors. In addition to the dioxetanes **2**, substantial amounts of the allylic hydroperoxides **8** are also formed in the photooxygenation by the ene reaction with singlet oxygen ($^1O_2$).[12] Electron-accepting groups (R^3 = Ac, CO_2Et) on the benzo ring promote the formation of the allylic hydroperoxides **8**, whereas electron-donating ones (R^3 = Me, tBu, OMe) favor the dioxetanes **2**.[11,13]

Chemical Transformations. The chemistry of the benzofuran dioxetanes **2** is presented in the rosette of Scheme 4. Due to their labile nature, generally the benzofuran dioxetanes **2** (R^1 = H, Me, Ph, R^2 = H, Me, Ph, R^3 = H, Me, tBu, Cl, Ac, Co_2Et, OMe) cleave at ambient temperatures to the corresponding keto esters **3** as major and 1-oxaspiro[2.5]octa-5,7-dien-4-ones **4** as minor products.[14] In the latter reaction, electron donors (R^3 = tBu, OMe) favor the formation of the spiroepoxides **4** by increasing the electron density of the aromatic system, whereas electron acceptors (R^3 = Ac, COOEt) facilitate the C–C cleavage to yield the keto esters **3** (Scheme 6).[15]

In contrast, upon treatment of the parent benzofuran dioxetane **2** (R^1 = R^2 = Me, R^3 = H) with catalytic amounts of tertraethylammonium bromide at 0 °C, the corresponding spiroepoxide **4** is formed quantitatively.[15] S_N2 attack of the bromide ion on the O-α atom of the peroxide bond is proposed as the mechanism, in which the resulting hypobromite intermediate **A** rearranges to the spiroepoxide **4** by



A (α-attack) **B** (β-attack)

(R^1 = R^2 = Me, R^3 = H)

opening of the furan ring and expulsion of the bromide ion through intramolecular nucleophilic attack of the phenolate ion on the O–Br bond. Alternatively, attack of Br^- on the O-β atom leads to intermediate **B**, and subsequent C–C cleavage affords product **3**.[15]

(11) (a) Berdahl, D. R.; Wassermann, H. H. *Isr. J. Chem.* **1983**, *409*–414. (b) Adam, W.; Albrecht, O.; Feineis, E.; Reuther, I.; Saha-Möller, C. R.; Seufert-Baumbach, P.; Wild, D. *Liebigs Ann. Chem.* **1991**, 33–40. (c) Adam, W.; Schulz, M. *Chem. Ber.* **1992**, *125*, 2455–2461.

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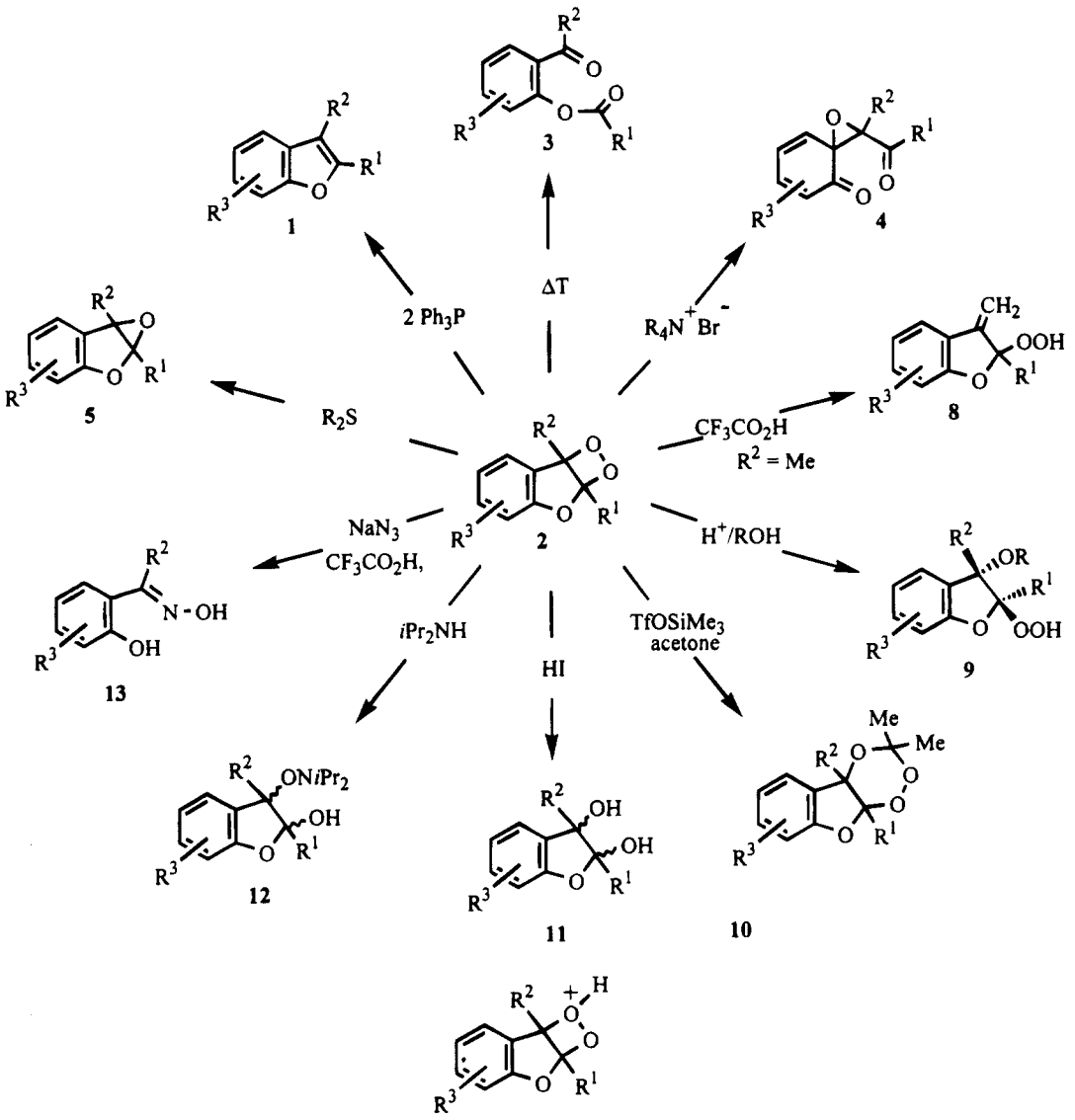
Scheme 4



On thermolysis, the labile spiroepoxides **4** (R^1 = Me, Ph, R^2 = Me, Ph, R^3 = H, tBu) rearrange to the benzodioxoles **14**, but at low temperature the dimers **15** are formed by Diels–Alder reaction (Scheme 7).[15] 4-Methyl-1,2,4-triazoline-3,5-dione (MTAD) gives the Diels–Alder adducts **16** with the spiroepoxide **4** (R^1 = R^2 = Me, R^3 = H).[15] Furthermore, nucleophilic addition of methanol at the R^2-substituted position of the spiroepoxide **4** (R^1 = R^2 = Me, R^3 = H) leads, under rearrangement, to the adduct **17**, a facile process which occurs even at room temperature and manifests the highly electrophilic nature and, thus, alkylation propensity of **4**.[14]

Acid-catalyzed rearrangement of the dioxetanes **2** (R^1 = R^2 = Me, R^3 = H, OMe) by trifluoroacetic acid produces the allylic hydroperoxides **8** in nearly quantitative yield (Scheme 4).[14] Addition of methanol and water to the benzofuran dioxetane **2** in the presence of catalytic amounts of trifluoroacetic acid affords highly diastereoselectively the corresponding *trans* adducts **9** (Scheme 4). The latter are formed by S_N2 attack of the nucleophile at the C-3 atom of the protonated dioxetane intermediate.[14]

Benzofuro-1,2,4-trioxane **10** (R^1 = Me, R^2 = Ph, R^3 = H) is obtained on treatment of the dioxetane **2** with acetone, catalyzed by trimethylsilyl trifluoromethanesulfonate (Scheme 4).[20] The latter persists in solution at room temperature for a few days and decomposes to the keto ester **3**, the dioxetane cleavage product.

Reduction of the benzofuran dioxetane **2** (R^1 = R^2 = Me, R^3 = H) by HI produces the 1,2-diol **11** (Scheme 4).[10a,19] Iodine is liberated in this process, which constitutes the well-established iodometric analysis of organic peroxides.

In contrast, the nucleophilic attack of diisopropylamine on the O-3 atom of the peroxide bond in the benzofuran dioxetane **2** (R^1 = R^2 = Me, R^3 = H) leads to the adduct **12** (Scheme 4). By elimination of hydroxylamine, the allylic alcohols are formed, probably by way of the intermediary benzofuran epoxide **5**.[15]

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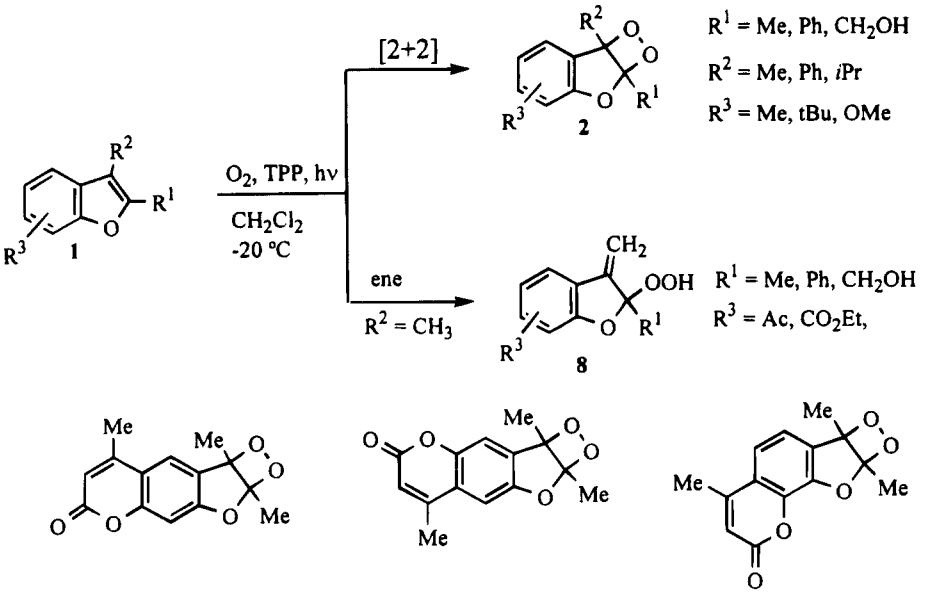
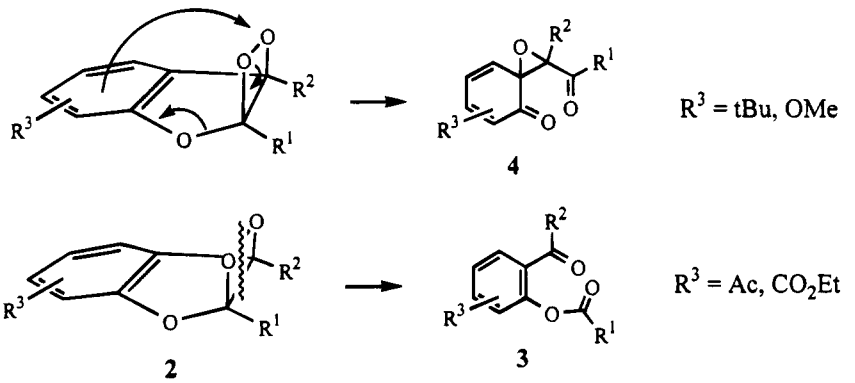
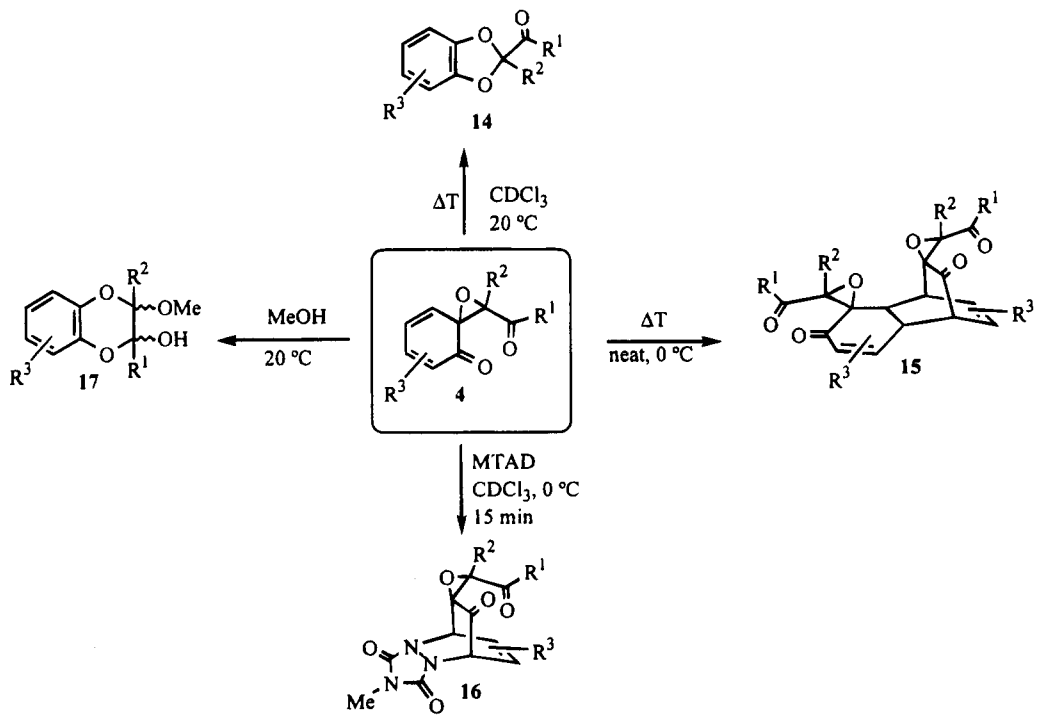
Scheme 5



Scheme 6



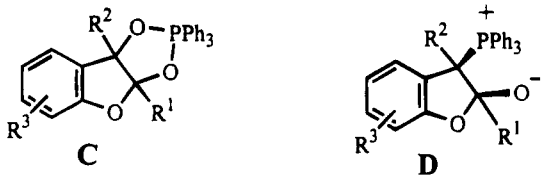
Scheme 7



The oxime **13** is the product of the CF_3CO_2H-catalyzed reaction of sodium azide[14] (Scheme 4) with the benzofuran dioxetane **2** ($R^1 = R^2 = Me$, $R^3 = H$). This complex transformation is also explained in terms of nucleophilic attack by the azide anion on the protonated dioxetane intermediate; however, the resulting azido hydroperoxide is too labile and fragments into the oxime **13**.[14]

On deoxygenation of the dioxetanes **2** ($R^1 = R^2 = Me$, $R^3 = H$) with sulfides, the benzofuran epoxides **5** result (Scheme 4). This transformation constitutes the first synthesis and spectral characterization of the labile benzofuran epoxides **5**.[14,16] Such deoxygenations are known reactions; however, catalytic decomposition of the dioxetanes prevails.[17] As we shall see later (Scheme 8), the independent synthesis of these unique epoxides can be achieved by dimethyldioxirane oxidation of the respective benzofurans **1**.[14,16]

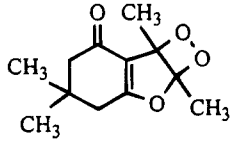
The reaction of benzofuran dioxetanes **2** ($R^1 = R^2 = Me$, $R^3 = H$, Ac, OMe) with excess Ph_3P affords the corresponding benzofurans **1** (Scheme 4).[18] A reasonable mechanism for this unprecedented deoxygenation of dioxetanes involves first biphilic insertion of Ph_3P into the peroxide bond to generate the labile phospholane **C**. Subsequent P–O bond scission and elimination of Ph_3PO lead to the corresponding epoxide **5** and/or the quinone methide **6**. Further nucleophilic addition of Ph_3P to benzofuran epoxide **5** or the quinone methide **6** gives the intermediate **D**, which on loss of Ph_3PO generates the benzofuran **1**.[18]



C **D**

($R^1 = R^2 = Me$, $R^3 = H$, Ac, OMe)

The related tetrahydrobenzofuran dioxetane (see below), the first furan dioxetane ever observed, exhibits chemistry similar to that displayed in the rosette of Scheme 4 for the benzofuran derivatives.[21] However, because of space limitations we shall not elaborate.



tetrahydrofuran dioxetane

The chemistry of the benzofuran dioxetanes **2** (Scheme 4) clearly reveals their propensity for alkylation and oxidation. Under acid catalysis, these relatively persistent dioxetanes act as carbon electrophiles, for which alkylation of the nucleophile proceeds by attack at the C-3 position. In the absence of acids, these strained peroxides manifest themselves as oxidants in that nucleophilic attack takes place at the O-3 heteroatom position. Thus, in the former process, alkylation of the DNA bases is expected, and in the latter, oxidation is expected. Whichever process prevails, DNA damage occurs with cytotoxic and mutagenic consequences, of which presumably the oxidative damage is the more serious one. In contrast, the thermal transformations are expected to be relatively harmless as concerns DNA damage, because on one hand the efficiency of triplet excited state production is quite low, while on the other hand the novel spiroepoxide **4** rearrangement products are rather ineffective in their alkylation of DNA.[8] The situation is different for the highly reactive benzofuran epoxides **5** and their valence-isomeric quinone methide **6**, which we shall take up now.

Benzofuran Epoxides 5 and Quinone Methides 6

Synthesis. The various benzofuran epoxides **5** ($R^1 = Me$, $R^2 = H$, Me, tBu, Ph, $R^3 = H$, Me, tBu, Ac, OMe) can be conveniently prepared in nearly quantitative yields by dimethyldioxirane (DMD) oxidation[23,24] (Scheme 8). As expected, electron-withdrawing substituents on the benzo moiety reduce the reactivity of the enolic double bond, as witnessed by longer reaction times and higher temperatures for complete conversion.[25] Fortunately, such epoxides are also more persistent and can, therefore, be more readily detected.

Epoxides **5** ($R^1 = Me$, $R^2 = H$, Me, tBu, Ph, $R^3 = H$, Me, tBu, OMe) are stable at −20 °C for spectral acquisition, but they decompose readily above 0 °C, which precludes their rigorous purification. Thus, the structure assignment of the epoxides rests entirely on NMR spectral data. The signals for the 2- and 3-methyl groups occur at ca. δ 1.80, which constitutes an expected upfield shift from the ca δ 2.40 for these methyl groups in the benzofurans **1**. Particularly diagnostic are the epoxide carbon atoms C-2 and C-3 at ca. δ 95 and 67 in the ^{13}C NMR *versus* ca. δ 154 and 110 for the corresponding olefinic carbon atoms of the benzofurans **1**.[25] Electron-donating groups, such as methoxy substituents, accelerate the rate of the epoxidation dramatically, and additionally an isomerization of the epoxides **5** to the quinone methides **6** is observed.[25] This rearrangement is analogous to that suggested for the furan epoxides into the enediones (Scheme 3).[26]

Chemical Transformations. The chemistry of these valence isomers is presented in the rosettes of Schemes 8 and 9. The former covers the rearrangements and isomerizations, the latter the cycloadditions and nucleophilic reactions.

Electronic and Steric Effects on the Product Distribution of the Epoxide 5 and Its Quinone Methide Valence Isomer 6

Whether the epoxides **5** or quinone methides **6** are observed in the oxidations of the benzofurans **1**

(23) (a) Adam, W.; Curci, R. *Chim. Ind.* **1981**, *63*, 20–28. (b) Adam, W.; Curci, R.; Edwards, E. O. *Acc. Chem. Res.* **1989**, *22*, 205–211. (c) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187–1201. (d) Curci, R. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI Press Inc.: Greenwich, 1990; Vol. 2, Chapter 1, pp 1–59. (e) Adam, W.; Hadjiarapoglou, L.; Curci, R.; Mello, R. In *Organic Peroxides*; Ando, W., Ed.; John Wiley and Sons, Chichester, 1992; pp 195–219. (f) Adam, W.; Hadjiarapoglou, L. In *Top. Curr. Chem.* **1993**, *164*, 45–62.

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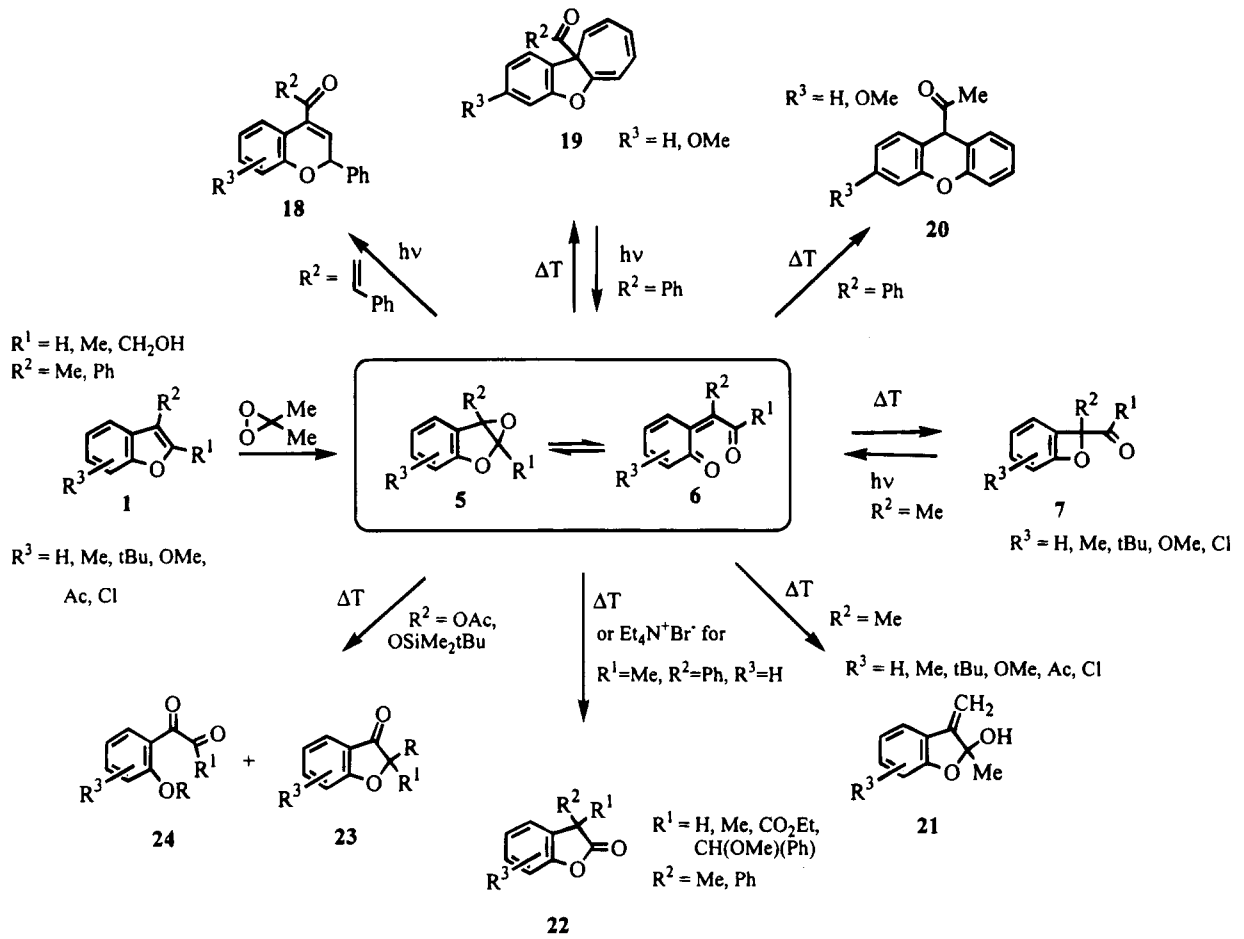
(26) Gingerich, S. B.; Jennings, P. W. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI Press Inc.; London, England, 1990; Vol. 2, pp 117–151.

Scheme 8



Scheme 9

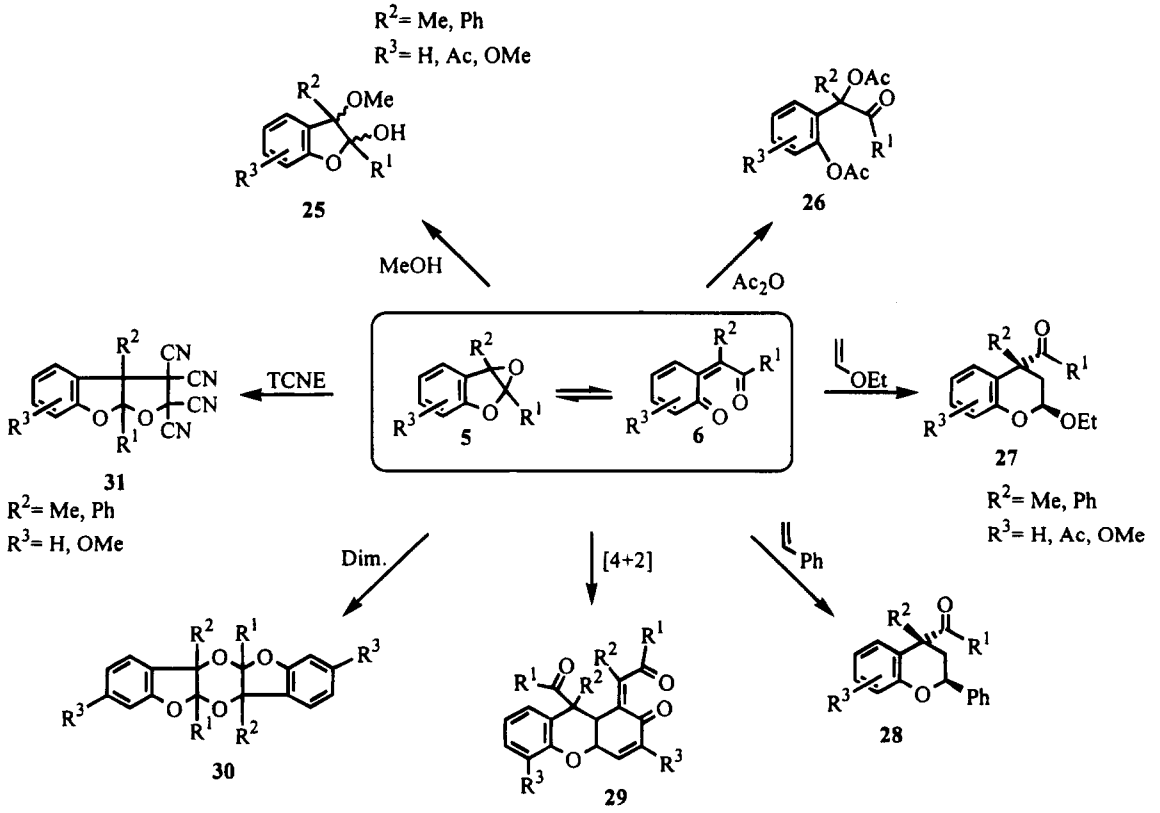
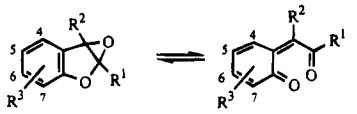


Table 1. Product Distributions[a] for the Dimethyldioxirane[b] Oxidation of Benzofurans 1



5 **6**

Entry	R^1	R^2	R^3	Product[c]
1	Me	Me	H	**5**
2	Me	Me	4-OMe	**5**
3	Me	Me	5-OMe	**5** : **6** (34 : 66)
4	Me	Me	6-OMe	**6**
5	Me	Me	7-OMe	**5** : **6** (57 : 43)
6	Me	Ph	H	**5**
7	Me	Ph	6-OMe	**6**

[a] Established by ^{1}H NMR, ca. 5% error of stated values. [b] Dioxirane (ca. 0.1 M) as acetone solution. [c] As observed quantitatively by NMR spectroscopy.

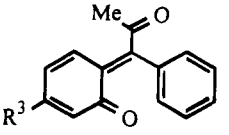
depends on the substituents.[25,27,28] For example, electron acceptors (R^3 = Ac, CO_2Et) favor the epoxides **5**, while electron donors (R^3 = tBu, OMe) favor the quinoid tautomers **6**. Moreover, the position of the substituent on the benzo ring determines which valence isomer dominates, as illustrated for the methoxy-substituted derivatives in Table 1. Thus, for the derivatives in entries 1, 2, and 6 the epoxides **5** are observed exclusively, while for those in entries 4 and 7 only the corresponding quinone methides **6** are detected.[27,28] The 5- and 7-methoxy regioisomers (entries 3 and 5) afford mixtures of **5** and **6** in proportions of 34:66 and 57:43.[27] Presumably electronic reasons are responsible for controlling the prevalence of the quinone methides **6** or the epoxides **5**. We propose that the 6-methoxy substituent para to the benzylic site in the epoxides **5** (entries 4 and 7) facilitates heterolysis of the epoxide ring through its (+M) effect by stabilization of the benzylic cation center, which is expected to promote valence isomerization to the quinone methides **6**.[27,28] For those benzofurans **1** which do not possess such electronic driving force (entries 1, 2, and 6), the epoxides **5** persist and these are observed NMR-spectrally.[27,28]

Reversible Valence Isomerization between Epoxides 5, Quinone Methides 6, and Benzoxetes 7

The various transformations in Schemes 8 and 9 convincingly demonstrate that a reversible valence isomerization operates between the colorless epoxide **5** and the deep-yellow quinone methide **6**. However, the query is whether these labile valence isomers **5** and **6** are in equilibrium with one another. Definitive proof for this was provided independently by way of the valence-isomeric benzoxetes **4** (Scheme 8).[27] Irradiation of mixtures of **5** and **6** in $CDCl_3$ at $\lambda > 400$ nm (sodium lamp) and −25 °C for 2−5 h generates the corresponding hitherto unprecedented benzoxetes **7** quantitatively.[27] On warming, the benzoxetes **7** revert to the same mixture of epoxides **5** and quinone methides **6** as obtained in the dioxirane oxidation of the benzofurans **1**. This observation provides unequivocal experimental proof that the epoxides **5** and quinone methides **6** are, indeed, in equilibrium with one another.[27]

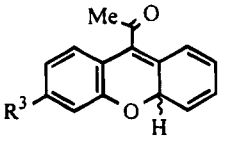
We shall now address the remaining unimolecular transformations in Scheme 8. On irradiation at −30 °C, quinone methide **6** (R^1 = Me, R^2 = styryl, R^3 = H) yields the hitherto unknown chromene **18** (Scheme 8). The formation of chromene **18** can be rationalized in terms of (*Z*)/(*E*) isomerization of the respective quinone methide **6**, and subsequent cyclization of the latter leads on aromatization to chromene **18**.[29]

Irradiation ($\lambda > 400$ nm) of the epoxide **5** (R^1 = Me, R^2 = Ph, R^3 = H) or the quinone methide **6** (R^1 = Me, R^2 = Ph, R^3 = 6-OMe) in acetone at −30 °C afforded nearly quantitatively the benzofurocycloheptatrienes **19**.[30] We propose that the mechanism for the formation of the cycloheptatrienes **19** is analogous to that reported by Bos.[31] First, valence isomerization of the benzofuran epoxides **5** leads to the quinone methides (*Z*)-**6**, which photoisomerize to their (*E*)-**6** diastereomers. Subsequent photolysis of the quinone methides (*E*)-**6** generates transient benzofuronorcaradienes, and thermal valence isomerization finally yields the cycloheptatrienes **19**.[30]



(*E*)-**6**

On thermal activation, the cycloheptatrienes **19** isomerize to the corresponding xanthenes **20** (Scheme 8) by way of the quinone methides (*E*)-**6**, i.e., the reverse of the photochemical sequence (*E*)-**6** → **19**. The rigorous structural assignment of the xanthenes rests on independent synthesis of **20** (R^1 = Me, R^3 = H), whose spectral data were identical to those of this compound formed on thermolysis of cycloheptatriene **19**.[30] At elevated temperatures, the *in situ* regenerated quinone methides **6** undergo electrocyclization to the intermediary chromenes. Sequential keto−enol tautomerization finally gives the corresponding xanthenes **20**.[30]



chromenes (R^3 = H, OMe)

The epoxides **5** and quinone methides **6** with a methyl group in the 3-position (R^2 = Me) rearrange at room temperature to the corresponding allylic alcohols **21** (Scheme 8), which are in equilibrium with their ring-opened tautomers.[14,16,27] While several

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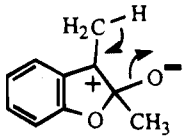
mechanisms may be considered for the formation of the latter, we suggest that the allylic alcohols **21** derive from transposition of a hydrogen atom in the 1,3 dipole of the ring-opened epoxide **5**. Alternatively, the quinone methides **6** may isomerize through 1,5-H shift to the ring-opened tautomers of the allylic alcohols **21**.



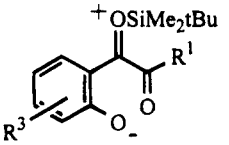
1,3 dipole

The epoxides **2** [R^1 = H, CO_2Et, CH(OMe)(Ph); R^2 = Me, R^3 = H] are too labile even for spectral observation; thus, on dioxirane oxidation only the corresponding benzofuranones **22** are obtained (Scheme 8).[32] Surprisingly, the respective allylic alcohols **21** are not found. Thus, irrespective of the electronic nature of the C-2 substituents, for these benzofuran epoxides **5** the 1,2 alkyl migration to the benzofuranones **22** is favored over the H abstraction by the epoxide oxygen atom from the C-3 methyl group to the allylic alcohols **21**.[32] In the case of the epoxide **5** (R^1 = CO_2Et), an ester group migrates during the formation of benzofuranone **22**. Related 1,2 shifts of electron-withdrawing groups (COR, COOR, COSR, $CONR_2$, etc.) have been observed for carbenium ions in Wagner–Meerwein rearrangements.[33]

In the presence of catalytic amounts (ca. 0.1 mol %) of tetraethylammonium bromide, the persistent epoxide **5** (R^1 = Me, R^2 = Ph, R^3 = H) gives on heating at 40 °C the respective benzofuran-2-one **22** (Scheme 8).[34] Presumably, the ammonium cation associates with the nucleophilic epoxide oxygen through electrostatic attraction and thereby facilitates the 2,3 methyl shift to the benzofuran-2-one **22** (R^1 = Me, R^2 = Ph, R^3 = H). In this context, the condensation of ethylene oxide with carbonyl compounds to the 1,3-dioxolanes, which is promoted by catalytic amounts of tetraethylammonium bromide, may be cited as evidence.[35]

The dioxirane oxidation of the 3-(acetyloxy)-2-methylbenzofuran **1** (R^1 = Me, R^2 = OAc) leads to the corresponding 3-benzofuranone **23** (R = Ac) and not to the expected epoxide **5** or the quinone methide **6** (Scheme 8).[29] The migration of the acetyl group in the corresponding benzofuran epoxide **5** to its 3-furanone **23** (R = Ac) is so facile that the labile epoxide **5** cannot be detected. Related isomerizations of epoxides to α-acetyloxy ketones have been reported.[36]

The oxidation of the silyloxy-substituted benzofuran **1** (R^1 = Me, R^2 = $OSiMe_2tBu$) with dimethyldioxirane affords the corresponding benzofuran-3-one **23** (R = $SiMe_2tBu$) and the diketone **24** (R = $SiMe_2tBu$) in a ratio of 83:17 (Scheme 8); the tautomers **23** and **24** do not interconvert.[29] This result is similar to the dimethyldioxirane oxidation of the more labile 2-methyl-3-(trimethylsiloxy)benzofuran.[37] The silyloxy-substituted 3-benzofuranone **23** is formed by silyl migration in the corresponding epoxide **5** analogous to 3-(acetyloxy)benzofuran.[29] Remarkable is the formation of diketone **24**, which may be formed through the dipolar structure of the silyloxy-substituted (*Z*)-**6**.[29]



dipolar structure of **24**

Let us now turn to the bimolecular transformations of the epoxides **5** and their valence-isomeric quinone methide **6** in Scheme 9. Of special interest in regard to DNA damage is the addition of nucleophiles to the derivatives R^1 = Me, R^2 = Me, Ph, R^3 = H, OMe. In methanol, even at −20 °C the hemiacetals **25** and their ring-opened tautomers are observed (Scheme 9).[27,28,34] This confirms once again the high alkylation propensity of these reactive epoxides. For comparison, arene oxides[38] require base or acid catalysis for nucleophilic addition, but the benzofuran epoxides **5** and their quinone methide valence isomers **6** react even at low temperatures without such assistance.

More significant, in connection with the alkylation of DNA by such highly electrophilic epoxides, are those derived from the furocoumarins **32**, namely, the naturally occurring parent psoralen (R = H) and its 8-methoxy derivative 8-MOP (R = OMe), *cf.* Scheme 10. Psoralen and 8-MOP are used extensively as photosensitizing agents for the treatment of skin deseases such as *psoriasis* in the so-called PUVA (psoralen + UVA) therapy.[39] While their usual action is photocyclization to the DNA bases,[40] more recently[41] it has been recognized that their malignancy derives also from alkylation of the DNA by the highly electrophilic epoxides postulated to be produced on metabolic oxidation. Indeed, our chemical model studies have confirmed that methyl(trifluoromethyl)dioxirane oxidation of 8-MOP at −50 °C affords the hitherto unknown labile epoxide (observed by low-temperature ^1H and ^{13}C NMR spectroscopy). Without acid or base catalysis the highly reactive 8-MOP epoxide adds methanol at −50 °C within a few minutes (Scheme 10).[42] This experiment unequivocally establishes such furocoumarin epoxides as potent alkylating agents of DNA, should they be generated in cells during oxidative metabolism.

The driving force for the methanol addition to these highly electrophilic epoxides may derive from aromatization during the Michael-type addition of the nu-

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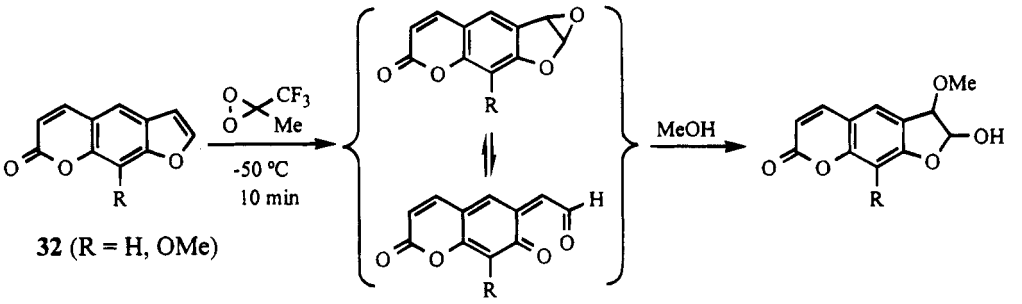
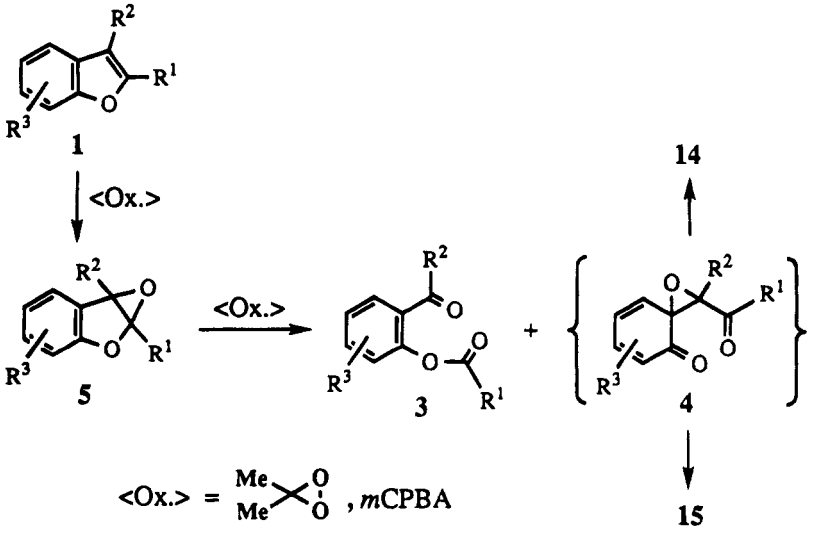
Scheme 10



Scheme 11



cleophile to the intermediary quinone methides **6** (R^1 = Me, R^2 = Me, Ph, R^3 = H, OMe) in the valence isomeric equilibrium **5** ⇌ **6**. The resulting ring-opened tautomer cyclizes subsequently to their hemiacetals **25** (Scheme 9). Since the stereochemical label is erased in this sequence of transformations, it is difficult to differentiate this mechanism from direct attack of methanol on the epoxide **5** (R^1 = Me, R^2 = Me, Ph, R^3 = H, OMe). In this respect, the reaction of benzofuran epoxide **5** (R^1 = Me, R^2 = Ph, R^3 = H) with freshly distilled acetic anhydride is relevant, in which at room temperature the diester **26** is obtained (Scheme 9).[34] The ring-opened structure of adduct **26** suggests that the addition of acetic anhydride proceeds through the quinoid valence isomer **6** rather than the epoxide **5**. Again, aromatization may serve as the driving force for the latter conjugate addition.

When the epoxides **5** and/or the quinone methides **6** (R^1 = Me, R^2 = Me, Ph, R^3 = H, Ac, OMe) are treated with an excess of ethyl vinyl ether, the Diels–Alder cycloadducts **19** (Scheme 9) are produced.[27,28,34] An X-ray structure analysis[34] of the [4 + 2] cycloadduct **19** (R^1 = Me, R^2 = Ph, R^3 = H) certifies the proposed structure. The initial (*Z*) stereochemistry of the quinone methides **6** is strictly conserved in the benzopyran cycloadducts **19**, as revealed by the X-ray structure.[34] Furthermore, the benzoxetes **7** also afford with ethyl vinyl ether the [4 + 2] cycloadducts **19** quantitatively.[34] Similarly, styrene gives with epoxide **5** (R^1 = Me, R^2 = Ph, R^3 = H) the [4 + 2] cycloadduct **28**, whose stereochemistry is identical to that of benzopyran **19** (Scheme 9). When left on its own at room temperature, the equilibrium mixture of epoxide **5** and its quinone methide **6** (R^1 = R^2 = Me, R^3 = 7-OMe) dimerizes to the [4 + 2] cycloadduct **29** (Scheme 9).[27]

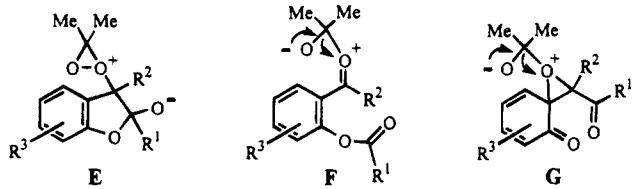
A remarkable transformation is observed for the quinone methide **6** (R^1 = Me, R^2 = Ph, R^3 = 6-OMe), for which not even traces of the corresponding epoxide **5** can be detected by NMR and which dimerizes to the dioxane **30** at room temperature (Scheme 9).[34] Related dimerizations of epoxides to dioxanes have been reported.[43] Again, minute amounts of the epoxide **5** must be in equilibrium with the quinone methide **6**, which then dimerizes through the ring-opened 1,3-dipolar structure to the dimer **30**. That such a resulting 1,3 dipole is a reasonable intermediate is supported by the fact that the quinone methides **6** (R^1 = Me, R^2 = Me, R^3 = 6-OMe) lead with tetracyanoethylene (TCNE) to the corresponding benzofurofurans **31** (Scheme 9).[34] A further example is the formation of furofuran **31** (R^1 = Me, R^2 = Ph, R^3 = H) on TCNE treatment of the corresponding epoxide **5** at −40 °C.[28,34]

Oxidations of Benzofuran Epoxides 5 and Quinone Methides 6

On treatment of the benzofuran **1** (R^1 = Me, R^2 = Ph, R^3 = H) with an excess of dimethyldioxirane at −20 °C, a mixture (ca. 80:20) of the respective dioxetane **2** decomposition products **3** and **14** (Scheme 11) is obtained.[20] In contrast, when the oxidation of this benzofuran **1** is performed with only 1 equiv of dimethyldioxirane at −70 to −20 °C, within 8 h the corresponding epoxide **5** is produced nearly quantitatively, as revealed by ^1H and ^{13}C NMR spectroscopy.[28,34] Moreover, in a control experiment, treat-

ment of the isolated epoxide **5** with dimethyldioxirane (1.5 equiv) at 0 °C affords the keto ester **3** and the benzodioxole **14** as well (Scheme 11). This constitutes the first oxygen atom transfer reaction from dimethyldioxirane to an epoxide![20]

To explain these unusual results, it must be stressed that the benzofuran oxides **5** figure as the most reactive epoxides known to date. Therefore, we postulate that in the above oxidation the transient dipolar form of the epoxide **2** is trapped by dimethyldioxirane to generate the intermediate **E**. The major reaction

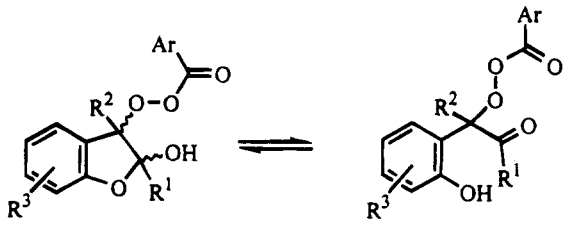


E **F** **G**

(R^1 = Me, R^2 = Ph, R^3 = H)

mode of the latter engages C–C bond cleavage to the keto ester **3** (Scheme 11) through intermediate **F** with concomitant elimination of acetone. As a minor pathway, C–O bond scission generates spiroepoxide **4** (Scheme 11) on loss of acetone through the intermediate **G**, and subsequently the labile spiroepoxide **4** rearranges to the catechol derivative **14** (Scheme 11). In this novel way, the dioxetane decomposition products **3** and **14** are formed in a ca. 85:15 ratio; however, the dioxetane **2** is not observed nor is it required. Indeed, a control experiment confirms that the authentic dioxetane **2** (R^1 = Me, R^2 = Ph, R^3 = H) persists under these reaction conditions.[20]

The reaction of parent benzofuran **1** (R^1 = Me, R^2 = Me, R^3 = H) with an excess (ca. 3 equiv) of water-free *m*-CPBA leads to the corresponding spiroepoxide dimer **15** (Scheme 11) as the main product.[44] An NMR experiment shows that the corresponding epoxide **5**, independently prepared by dimethyldioxirane epoxidation, gives on treatment with 1 equiv of *m*-CPBA at −50 °C in $CDCl_3$ first a mixture of the intermediary *m*-CPBA adduct **H** and its ring-opened tautomer **H′**.



H **H′**

(R^1 = Me, R^2 = Me, Ph, R^3 = H)

On warmup to room temperature, the corresponding cycloaddition dimer **15** is observed,[44] for which the spiroepoxide **4** serves as precursor and is produced from the peracid adduct **H′** analogous to the hypobromite **A** (see above).

2-Methyl-3-phenylbenzofuran **1** (R^1 = Me, R^2 = Ph, R^3 = H) also affords with *m*-CPBA (2.2 equiv) the dioxetane C–C cleavage product **3**, together with the benzodioxole **14** (Scheme 11) in a ratio of 69:31.[44] Authentic samples of the cleavage product **3** and 1,3-benzodioxole **14** were prepared by thermolysis of the dioxetane **2**.

The rosettes in Scheme 8 and 9 summarize the abundant and in most part unprecedented chemistry of the benzofuran epoxides **5** and their valence-isomeric quinone methides **6**. Precisely the fact that these valence isomers coexist with one another in the equilibrium **5** ⇌ **6** accounts for the high reactivity and complexity of these epoxides in regard to their chemical behavior. While the various cycloaddition reactions establish the reversibility between the epoxides **5** and quinone methides **6**, the hitherto unknown benzoxetes **7** figure as keystones in the mosaic of rich chemistry in that they unequivocally confirm the existence of an authentic equilibrium. The high reactivity and, thus, low persistence (most of the epoxides **5** and quinone methides **6** can be detected NMR-spectrally only at subambient conditions) we ascribe to the strongly electrophilc nature of the epoxides **5** and quinone methide valence isomers **6**. Consequently, nucleophilic addition of methanol or acetic anhydride proceeds very fast (minutes) with these electrophiles at temperatures even as low as −60 °C without acid or base catalysis! That these epoxides and quinone methides serve as potent DNA-alkylating agents is no longer surprising.

The unique and unusual feature of the benzofuran epoxides **5** is the fact that they are more reactive and less persistent than the corresponding dioxetanes **2**. The latter can be isolated and handled at room temperature, and addition of nucleophiles (methanol) requires acid catalysis. In fact, while the benzofuran epoxides **5** are the most reactive epoxides known to date and function as alkylative agents, the corresponding dioxetanes **2** act primarily as oxidants. Whichever the chemical mode of action, both the benzofuran dioxetanes **2** and epoxides **5** are potent DNA-damaging substances with cytotoxic and mutagenic consequences.[10a] In this context we have elucidated the chemistry of these highly reactive molecules and provide herewith the essential background to understand their biological behavior. Future efforts should address the challenge of preparing sufficiently persistent furan epoxides (to date none are known!) for detection and isolation.

Our work in this area was generously supported by the Deutsche Forschungsgemeinschaft (SFB 172: "Molekulare Mechanismen kanzerogener Primärveränderungen"), Fonds der Chemischen Industrie, and the Alexander von Humboldt Foundation. The co-workers, whose names are given in the cited references, deserve special praise and appreciation for their diligence, imagination, motivation, and perseverance.

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