Unprecedented Formation of a Cyclic Tetramer from the Acidolysis of Indene Ozonide. Isolation and Characterisation of a Novel Dodecaoxacycloicosane Derivative

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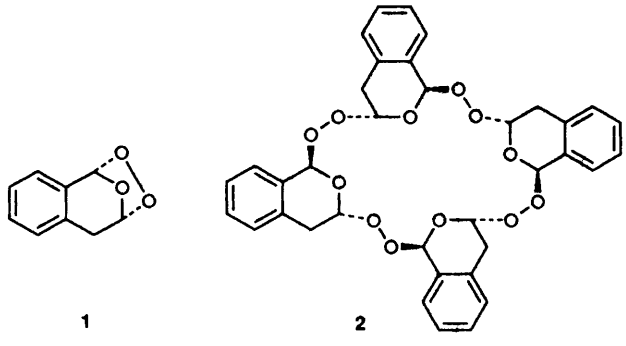
Treatment of indene ozonide with chlorosulfonic acid in methylene chloride at 0 °C affords a crystalline tetramer of the ozonide, the structure of which is shown by X-ray crystallographic analysis to contain a novel 20-membered dodecaoxacycloicosane ring system.

Recent renewed interest in the chemsitry of cyclic peroxides has been stimulated by the potent pharmacological activity exhibited by a variety of naturally occurring cyclic peroxides.[1] Simpler synthetic mono-[2] and poly-[3] cyclic peroxide systems have also been shown to possess significant biological activity.

Ozonides (1,2,4-trioxolanes) derived from either the conventional reaction of ozone with olefins or the photooxygenation of furans, have been shown to be useful, if unexpected, precursors of a range of peroxide systems including 1,2,4,5,7-pentaoxocanes,[4] 1,2,4,5-tetroxanes,[4] and 1,2,4,6,7,9-hexaoxecanes.[5] We now report the isolation and characterisation of a novel cyclic tetrameric product obtained from the acidolysis of the monomeric ozonide derived from indene **1**.[6]

Treatment of indene ozonide **1** with chlorosulfonic acid (0.1 equiv.) in methylene chloride at 0 °C for 4 h followed by trituration of the crude product mixture with hexane gave a colourless, highly crystalline compound **2** in *ca.* 20% yield.†

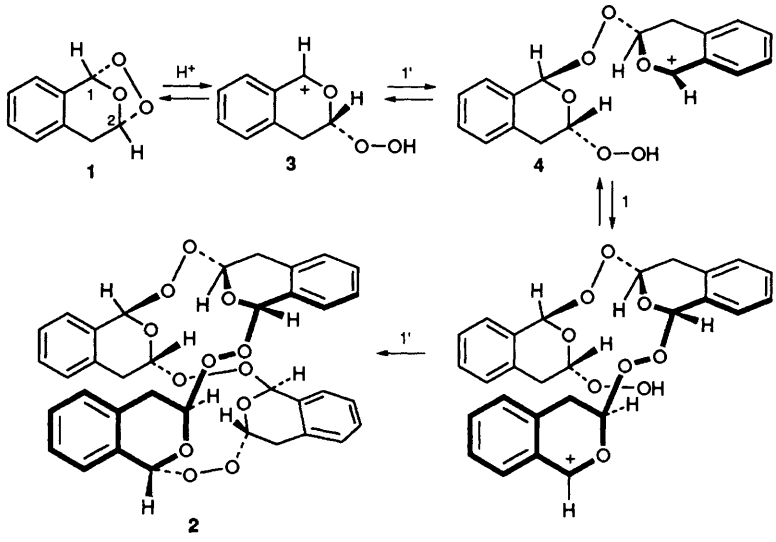
Although the analytical data‡ were generally consistent with compound **2** being a cyclic oligomer of ozonide **3**, its molecular



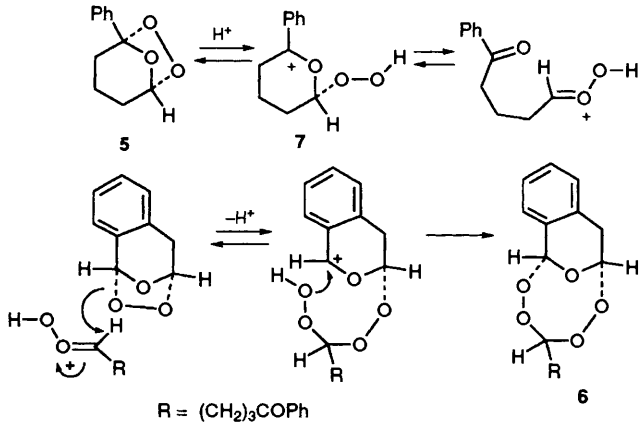
1 **2**

† The byproduct was an acyclic polyozonide similar to that obtained from the ozonolysis of indene in methylene chloride; m.p. 100–103 °C (from ether/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz, $SiMe_4$) δ 2.7–3.5 (br s), 5.5–6.6 (br s), 6.9–7.9 (br s), the ratio of the peak areas being 1:1:2; molecular mass (vapour-pressure osmometery) 1067.5; IR (KBr) 3600–3200, 1720, 1690, 1600, 1480, 1320, 1200, 1090, 750, 670 cm^{-1}.

‡ Compound **2**: m.p. 202–205 °C (from CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz, $SiMe_4$) δ 2.61 (d, *J* 4 Hz, 4 H), 2.64 (d, *J* 10 Hz, 4 H), 5.85 (dd, *J* 10 and 4 Hz, 4 H), 6.32 (s, 4 H), 6.5–7.2 (m, 16 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.94, 98.98, 101.22, 126.30, 126.96, 127.63, 128.94, 129.98, 129.98, 132.51; IR (KBr) 1320, 1065, 1010, 960, 740 cm^{-1}. Satisfactory elemental analysis obtained.



Scheme 1



Scheme 2

structure could only be determined unambiguously by X-ray crystallographic analysis.§

As depicted in Fig. 1, compound **2** turns out to be a highly symmetrical cyclic tetramer of ozonide **1** having a twofold axis of symmetry and containing a 20-membered, tub-shaped dodecaoxacycloicosane ring system, which is, to our knowledge, the largest stable macrocyclic peroxide system identified to date. In addition, four hydrogen atoms, each formerly at the bridgehead position 2 in **1**, are located inside the ring system (Fig. 2) and the relative configuration at the other bridgehead position in **1** has been inverted during the cyclisation reaction. It follows, therefore, from the structure of **2** that the cyclotetramerisation of **1** must be a remarkably stereoselective process.

A plausible mechanism for the direct formation of **2** from **1** is outlined in Scheme 1. This intrinsically requires that the individual enantiomers of **1**, in which the two bridgehead carbon centres 1 and 2 are chiral but of opposite relative stereochemistry, are incorporated into the growing intermediate in a strictly alternating sequence.¶ A selective acid-catalysed ring opening of **1** would produce carbocation **3**, which would in turn selectively induce the ring opening of a second enantiomeric molecule of the ozonide (**1'**) by the least sterically hindered approach to give **4** inverting the relative configuration at 1 and establishing the *anti*-relationship between the peroxy moieties as is evident in the structure of **2**. In the corresponding third and fourth steps of the sequence, the isochromanyl ring systems of ozonide molecules **1** and **1'** must stack essentially parallel to those of the first and second sub-units, respectively, minimising intramolecular steric interactions and allowing the growing acyclic intermediate to coil round thereby facilitating cyclisation to **2**. The cyclisation process in this instance is also favoured by the fact the hydrogens atoms located at each of the centre corresponding to position 2 in **1** have a minimal steric requirement.

Under similar reaction conditions, the analogous 1-phenylcyclopentene ozonide **5** undergoes dimerisation to give a 2,3,5,6,11-pentaoxabicycloundecane (55%) together with a small amount of a 1,2,4,5-tetroxane (7%).[7] Likewise, a mixture of ozonide **5** and indene ozonide **1** produced the

§ *Crystal data* for compound **2**: $C_{36}H_{32}O_{12}$, M = 656.6, colourless prisms, monoclinic, space group *C2/c* (No. 15), a = 14.4074(11), b = 14.4673(4), c = 14.9681(15) Å, β = 96.370(10)°, U = 3100.6 Å^3, Z = 4, D_c = 1.401 g cm^{-3}, $F(000)$ = 1376, μ(Mo-Kα) = 0.99 cm^{-1}.

The intensity data were collected on an Enraf-Nonius FAST area detector diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.710693 Å). Further details of the instrumental settings have been published elsewhere.[8] Of the 3777 unique data measured, 1257 had $I > 2\sigma(I)$ and were used in subsequent structure solution and refinement. The intensity data were corrected for Lorentz and polarisation, but not for absorption. The structure was solved by direct methods (SHELXS86[9]) and refined by full-matrix least-squares methods using anisotropic temperature factors for the non-hydrogen atoms (SHELX76[9]). At convergence, the discrepancy indices R and R_w were 0.032 and 0.044 where $w^{-1} = [\sigma^2(F) + 0.00674\,F^2]$. The final difference Fourier map contained no feature greater than ±0.15 e Å^3.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

¶ Other reaction sequences would require re-equilibration of stereochemsitry at the carbon centres corresponding to 1 and 2 in **3** in order to produce **4**. Although this is possible under the acidic reaction conditions, it is more likely that these alternative pathways will contribute substantially to the formation of acyclic polyozonides.

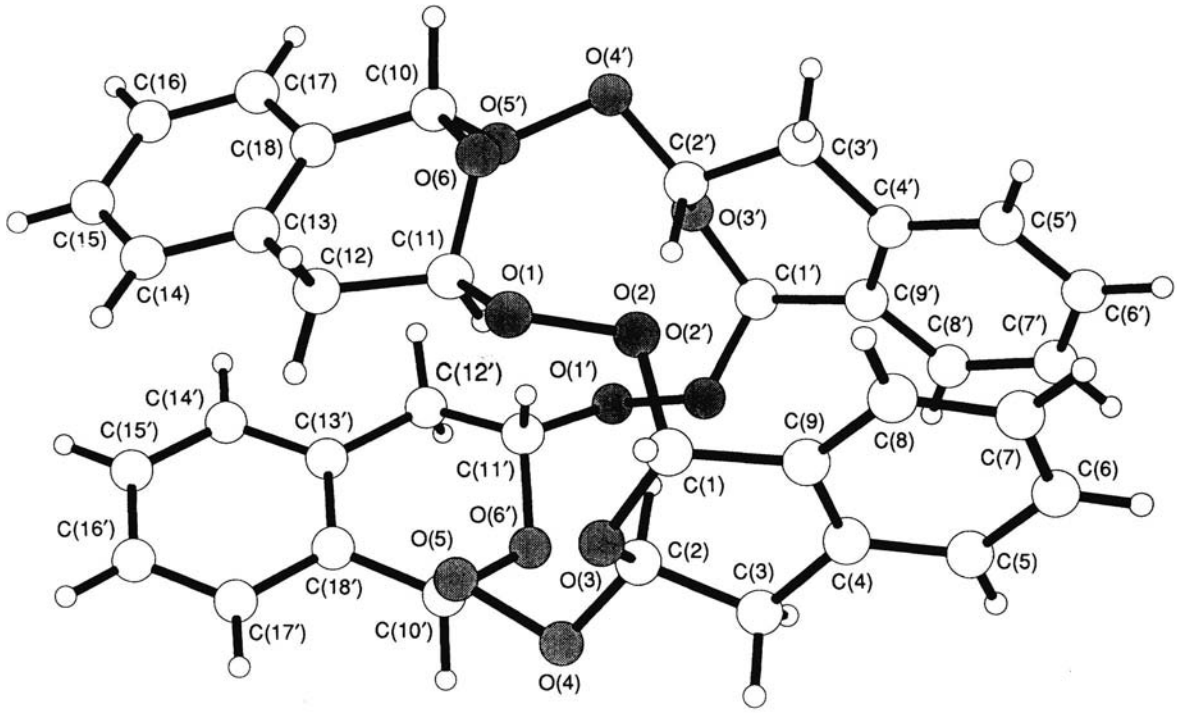


Fig. 1 The crystal and molecular structure of tetrameric peroxide **2**

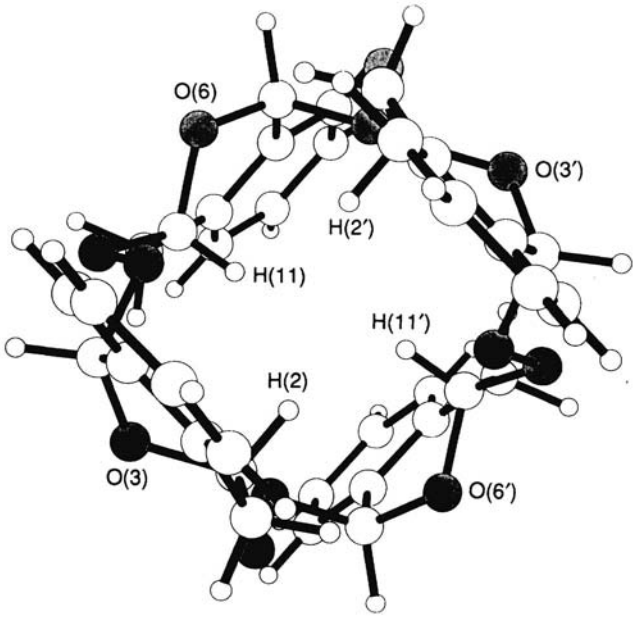


Fig. 2 View of cyclic peroxide **2** along the twofold symmetry axis

cross-dimerization product **6**‖ (38%) suggesting that the attack of the carboxonium ion intermediate **7**, derived from ring opening of **5**, on ozonide **1** is followed by immediate ring closure (Scheme 2).[4]

These observations support the notion that on ring opening of indene ozonide **1**, the isochromanyl ring systems in the resulting intermediate carbocations (Scheme 1) remain intact and consequently have significantly different steric requirements from the corresponding intermediates derived from ozonide **5** which may be more acyclic in nature and hence behave like protonated carbonyl oxides (Scheme 2). Thus, ozonide **1** produces the tetramer **2** whereas ozonide **5** undergoes self- or cross-dimerisation more readily.

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‖ Bicyclopentaoxabicycloundecane **6**: an oil; ^{1}H NMR ($CDCl_3$, 400 MHz, $SiMe_4$) δ 1.7–1.8 (m, 2 H), 1.93 (quintet, *J* 7 Hz, 2 H), 2.85 (d, *J* 19 Hz, 1 H), 3.03 (t, *J* 7 Hz, 2 H), 3.32 (dd, *J* 19 and 7 Hz, 1 H), 5.62 (t, *J* 6 Hz, 1 H), 5.80 (d, *J* 7 Hz, 1 H), 6.22 (s, 1 H), 7.1–7.6 (m, 7 H), 7.8–8.0 (m, 2 H); ^{13}C NMR ($CDHCl_3$, 100 MHz) δ 19.31, 27.36, 27.97, 37.73, 96.86, 97.26, 108.88, 126.65, 127.12, 127.42, 127.94, 127.98, 128.50, 128.55, 128.92, 130.12, 130.36, 133.01, 136.82, 199.26; IR 2940, 1680, 1115, 750 cm^{-1}; satisfactory elemental analysis obtained.

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