

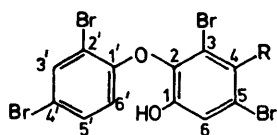
Structural Studies of Halogenated Diphenyl Ethers from a Marine Sponge

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The structures of two halogenated diphenyl ethers from a marine sponge have been assigned from spectroscopic and X-ray crystallographic evidence. The two compounds have been identified as 3,5-dibromo-4-chloro-2-(2,4-dibromophenoxy)phenol (1) and 3,5-dibromo-2-(2,4-dibromophenoxy)phenol (2).

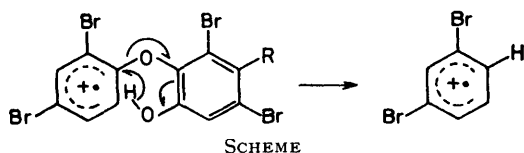
As part of a programme to investigate the natural products of marine organisms occurring off the Western Australian coast we have examined the constituents of an unidentified sponge collected near Rottnest Island.† The two major constituents have been shown to be the new halogenated biphenyl ethers (1) and (2) and their structure has been secured by X-ray crystallographic analysis.

Extraction of a diced sample of the sponge with organic solvents yielded a semi-crystalline extract which contained two major components, separable by column chromatography on alumina. The more polar component (1) (1.3% of the dry weight of the sponge), m.p. 181–181.5 °C, $C_{12}H_5Br_4ClO_2$, showed signals in the n.m.r.



- (1) R = Cl
(2) R = H

spectrum attributable to protons on isolated 1,2,4- and penta-substituted aromatic rings and an exchangeable phenolic proton. The phenolic hydroxy-group was located on the pentasubstituted ring since a shift to higher field of 0.51 p.p.m. was observed for the single aromatic proton in the n.m.r. spectrum of the sodium salt of (1) and this also suggests¹ that the ring proton is *ortho* or *para* to the hydroxy-group. This information indicates that the second oxygen is involved in an ether linkage and the presence of a 2-(2,4-dibromophenoxy)-phenol system was inferred from the mass spectrum which showed significant peaks at m/z 234, 236, and 238 ($C_6H_4Br_2$) probably arising from the rearrangement of the molecular ion as shown in the Scheme.² Since the



position of the chlorine could not be readily assigned, an

† A specimen has been deposited with the Western Australian Museum (catalogue no. WAM 403-80).

X-ray analysis of the compound was undertaken (see later). The results indicate the structure to be 3,5-dibromo-4-chloro-2-(2,4-dibromophenoxy)phenol (1).

The less polar component (2) (1.2% of the dry weight of the sponge), m.p. 172.5–173 °C, $C_{12}H_6Br_4O_2$, was assigned the structure 3,5-dibromo-2-(2,4-dibromophenoxy)phenol on the following evidence. The n.m.r. spectrum showed signals for an exchangeable phenolic proton and aromatic protons which, from INDOR analysis, were assigned to two mutually independent aromatic rings with 1,2,4- and 1,2,3,5-substitution patterns. The n.m.r. spectrum of the sodium salt showed that two *meta*-coupled protons were shifted to higher field by 0.84 and 0.92 p.p.m., thus locating these *ortho*- and *para*- to the phenolic hydroxy-group.¹ The mass spectrum also showed significant peaks at m/z 234, 236, and 238 as observed for (1) (Scheme). An X-ray crystallographic analysis confirmed the structure assigned to (2).

Brominated derivatives of 2-phenoxyphenol have been isolated^{3,4} earlier from the sponge *Dysidea herbacea* collected in the Western Caroline Islands and have been detected⁵ in samples of *D. herbacea* from the Great Barrier Reef. The structure of the pentabromo-derivative, analogous to (1), has been secured by synthesis.⁴ A preliminary examination of the sponge from Rottnest Island, W.A., indicates that it is not a *Dysidea* species.‡

EXPERIMENTAL

General experimental details have been reported previously.⁶ In addition, ¹³C n.m.r. spectra were recorded with a Bruker Spectrospin instrument operating at 20.1 MHz.

For t.l.c., silica gel plates (5 × 20 cm, 0.25 mm) were used with CH_2Cl_2 -EtAc (3 : 1 v/v) as developing solvent.

Isolation of Diphenyl Ethers (1) and (2).—A freshly frozen specimen of the sponge was finely diced and dried *in vacuo* at 40 °C overnight. The dried sample (66 g) was ground to a fine powder and exhaustively extracted with light petroleum CH_2Cl_2 , and MeOH to yield semicrystalline oils (2.2, 1.8, and 4.9 g, respectively). T.l.c. showed that all fractions contained a mixture of two main components. Elution (light petroleum- $CHCl_3$) of the light petroleum extract through a column of alumina (neutral, activity III, 60 g) gave fractions containing crystalline samples of (2) (192 mg) and (1) (205 mg).

‡ We are grateful to Dr. C. Wilkinson, Australian Institute of Marine Science, Townsville, for this information.

3,5-Dibromo-4-chloro-2-(2,4-dibromophenoxy)phenol (1) was recrystallized from CHCl_3 as prisms, m.p. 181.0–181.5 °C (Found C, 26.75; H, 0.95; Br, 59.6; Cl, 6.6. $\text{C}_{12}\text{H}_5\text{Br}_4\text{ClO}_2$ requires C, 26.88; H, 0.94; Br, 59.6; Cl, 6.6%); λ_{max} (EtOH) 285 nm (ϵ 5 500); ν_{max} (Nujol) 3 505, 3 420, 1 585, 890, 870, 860, 840, and 820 cm^{-1} ; δ (90 MHz; CDCl_3) 5.6br (s, OH), 6.40 (d, J 8.5 Hz, 6'-H), 7.29 (dd, J 2.0 and 8.5, 5'-H), 7.41 (s, 6-H), and 7.79 (d, J 2.0, 3'-H). The n.m.r. spectrum of the sodium salt of (1) in $[\text{}^2\text{H}_6]\text{dimethyl sulphoxide}$ ($[\text{}^2\text{H}_6]\text{DMSO}$) showed the following signals {values for corresponding signals for (1) in $[\text{}^2\text{H}_6]\text{DMSO}$ are in parentheses}: δ 6.44 [d, J 9.1 Hz (6.53)], 6.87 [s (7.38)], 7.35 [dd, J 2.3 and 9.1 Hz (7.39)], and 7.80 [d, J 2.3 Hz (7.90)]; δ_{C} (20.1 MHz; CDCl_3) 152 (s), 148.7 (s), 140.0 (s), 136.5 (d), 131.7 (s), 127.8 (d), 120.8 (d), 120.5 (s), 118.9 (s), 116.9 (s), 115.9 (d), and 112.9 (s); m/z 542, 540, 538, 536, 534, 532 (M^+ , 94%), 380, 378, 376, 374 ($M^+ - 2\text{Br}$, 100), 344, 342, 340, 338 ($M^+ - 2\text{Br} - \text{HCl}$, 12), 269, 267 (18), 238, 236, 234 (35), and 75 (53).

3,5-Dibromo-2-(2,4-dibromophenoxy)phenol (2) was recrystallized from CHCl_3 as prisms, m.p. 172.5–173 °C (Found: C, 28.65; H, 1.34; Br, 63.3. $\text{C}_{12}\text{H}_6\text{Br}_4\text{O}_2$ requires C, 28.72; H, 1.21; Br, 63.7%), λ_{max} (EtOH) 291 nm (ϵ 4 700); ν_{max} (Nujol) 3 505, 1 595, 1 572, 1 428, 920, 871, 843, 814, 759, and 720 cm^{-1} ; δ (90 MHz; CDCl_3) 5.65br (s, OH), 6.43 (d, J 9.0 Hz, 6'-H), 7.20 (d, J 2.2 Hz, 4-H), 7.28 (dd, J 3.0 and 9.0 Hz, 5'-H), 7.33 (d, J 2.2 Hz, 6-H), and 7.77 (d, J 3.0 Hz, 3'-H). The n.m.r. spectrum of the sodium salt of (2) in $[\text{}^2\text{H}_6]\text{DMSO}$ showed the following signals {values for corresponding signals for (2) in $[\text{}^2\text{H}_6]\text{DMSO}$ are in parentheses}: δ 6.29 [d, J 2.3 Hz (7.13)], 6.42 [d, J 2.3 Hz (7.34)], 6.43 [d, J 9.2 Hz (6.46)], 7.33 [dd, J 2.3 and 9.2 Hz (7.41)], and 7.72 [d, J 2.3 Hz (7.87)]; δ_{C} (20.1 MHz, $[\text{}^2\text{H}_6]\text{acetone}$) 154.2 (s), 153.0 (s), 140.0 (s), 136.4 (d), 132.4 (d), 127.3 (d), 120.9 (d), 119.9 (s), 118.9 (s), 116.9 (d), 115.2 (s), and 113.1 (s); m/z 506, 504, 502, 500, 498 (M^+ , 65%), 344, 342, 340 ($M - 2\text{HBr}$, 100), 238, 236, 234 (30), 126 (40), and 75 (80).

Crystallographic Analyses.—*Crystal data.* (1): $\text{C}_{12}\text{H}_5\text{Br}_4\text{ClO}_2$, $M = 536.3$. Monoclinic, space group $P2_1/c$ (C_{2h}^5 , No. 14), $a = 7.850(5)$, $b = 8.694(6)$, $c = 21.13(1)$ Å, $\beta = 92.6(1)^\circ$, $U = 1 321(2)$ Å³, $Z = 4$, $D_m = 2.46(1)$, $D_c = 2.47$ g cm^{-3} , $F(000) = 1 000$, $\mu_{\text{Mo}} = 128$ cm^{-1} . Specimen size: $0.24 \times 0.23 \times 0.09$ mm.

(2): $\text{C}_{12}\text{H}_6\text{Br}_4\text{O}_2$, $M = 501.8$. Monoclinic, space group $P2_1/c$ (C_{2h}^5 , No. 14), $a = 21.57(1)$, $b = 8.060(4)$, $c = 8.082(6)$ Å, $\beta = 93.19(5)^\circ$, $U = 1 403(2)$ Å³, $Z = 4$, $D_m = 2.36(1)$, $D_c = 2.38$ g cm^{-3} , $F(000) = 936$, $\mu_{\text{Mo}} = 113$ cm^{-1} . Specimen size: $0.05 \times 0.18 \times 0.16$ mm.

Structure determination. Unique data sets were measured at 295(1) K to $2\theta_{\text{max}} 45^\circ$ for both structures on a Syntex $P2_1$ four-circle diffractometer equipped with monochromatic $\text{Mo-K}\alpha$ radiation ($\lambda = 0.710 69$ Å), using a conventional $2\theta/\theta$ scan mode, yielding 1 931(1), 1 834(2) independent reflections; of these 1 153(1), 1 052(2) with $I > 3\sigma(I)$ were considered 'observed' and used in the refinement of the structure after correction for absorption. The structures were solved by direct methods. Refinement was by full-matrix least-squares methods, anisotropic thermal parameters being employed for the non-hydrogen atoms. Hydrogen-atom positional parameters were estimated at the trigonal values for the aromatic hydrogen atom and constrained, with U_{H} set at $1.25 < U_{\text{ii}}$ (parent carbon); phenolic hydrogen atoms were located in difference maps and 'improved' to reasonable bond lengths and angles and

constrained similarly. Residuals at convergence were (R , R' , S): 0.040, 0.045, 1.2, (1); 0.061, 0.074, 1.9, (2), reflection weights being $[\sigma^2(F_o) + 0.005(F_o)^2]^{-1}$. Computation was carried out using the X-RAY 76 program system⁷ implemented on a Perkin-Elmer 8/32 computer by S. R. Hall. Neutral-atom scattering factors were employed, those for the non-hydrogen atoms being corrected for anomalous dispersion (f' , f'').⁸⁻¹⁰ Atom numbering is shown in Figure 1, halogen, hydrogen, and phenol oxygens corresponding to the parent carbon; the scheme for the crystallographic work does not correspond to the above, all

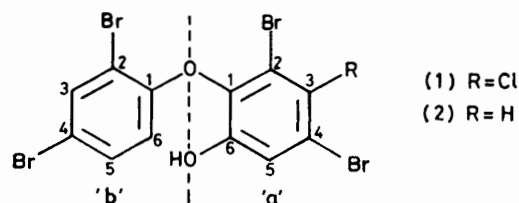


FIGURE 1 Crystallographic numbering scheme for compounds (1) and (2)

rings being numbered from the ether for compactness of tabulation.

Hydrogen atom parameters, thermal parameters, structure factor amplitudes, and least squares planes are available as Supplementary Publication No. SUP 23094 (17 pp.).*

DISCUSSION

Single crystal X-ray structure determinations assign the molecular structures as given above for (1) and (2); in each case the asymmetric unit of the monoclinic cell is a single discrete molecule. As might be expected within each of the molecules of (1) and (2), potential interactions between the substituents *ortho* to the ether linkage preclude coplanarity of the phenyl ring planes, since the angle at the central ether oxygen, as is usual, lies close to 120° . In fact, the phenyl rings are more nearly normal to each other, the interplanar dihedral angles being 85 and 86° for (1) and (2) respectively. The relative positions of segments, a,b is similar, being shown by consideration of the fact that in (1), C(1b) lies 1.08 Å out of the plane of the 'a' section C_6 entity, while C(1a) is 0.21 Å out of the corresponding 'b' plane; in (2), C(1b) is 1.09 Å out of the 'a' plane, while C(1a) is 0.33 Å out of the 'b' plane. Possible consequential differences in C(1)–O(0) distances arising from the variations in relative tilt of the C(1a)–O–C(1b) and phenyl ring planes are indeterminate in terms of the precision of the present measurements, this being relatively low for the C–O distances because of the high 'heavy atom' content in both cases. We note, however, that in both (1) and (2) the phenolic oxygen lies well away from the plane of the 'b' phenyl ring of the molecule, the phenolic hydrogen atoms presumably hydrogen bonding intermolecularly (see below) rather than interacting with the adjacent

* For details, see Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 2*, Index issue, 1980.

TABLE I

Non-hydrogen atom co-ordinates for (1) and (2) (the phenolic hydrogen is included, however)

Atom	(1)			(2)		
	<i>x</i>	<i>y</i>	<i>z</i>	<i>x</i>	<i>y</i>	<i>z</i>
O(0)	0.080 3(9)	0.322 3(9)	0.414 8(4)	0.252 3(7)	-0.107 0(15)	0.314 9(14)
Ring a						
C(1)	0.146 9(13)	0.222 4(12)	0.459 7(5)	0.309 8(9)	-0.039 1(21)	0.292 9(21)
C(2)	0.187 1(13)	0.073 1(13)	0.442 8(6)	0.349 2(9)	0.006 6(22)	0.425 6(24)
Br(2)	0.163 5(2)	0.018 9(2)	0.357 37(6)	0.320 8(1)	-0.015 1(3)	0.645 7(2)
C(3)	0.247 5(14)	-0.030 0(13)	0.488 1(6)	0.405 7(9)	0.065 5(23)	0.413 1(21)
Cl(3)	0.300 3(4)	-0.215 1(3)	0.467 8(2)			
C(4)	0.261 6(13)	0.016 1(13)	0.551 0(6)	0.427 4(9)	0.078 8(20)	0.251 2(25)
Br(4)	0.340 5(2)	-0.115 3(2)	0.615 10(7)	0.508 3(1)	0.163 8(3)	0.219 4(3)
C(5)	0.215 6(14)	0.163 2(14)	0.568 0(6)	0.391 2(9)	0.035 1(21)	0.113 7(22)
C(6)	0.159 6(13)	0.269 2(13)	0.522 7(5)	0.330 3(8)	-0.024 8(21)	0.133 9(23)
O(6)	0.118 4(10)	0.413 6(8)	0.537 7(5)	0.293 1(6)	-0.064 5(15)	0.004 0(14)
H(6)	0.220(-)	0.485(-)	0.540(-)	0.312(-)	-0.154(-)	-0.050(-)
H(6')	-0.010(-)	0.410(-)	0.507(-)			
Ring b						
C(1)	0.190 0(14)	0.413 2(13)	0.382 5(6)	0.202 6(9)	-0.001 4(24)	0.324 6(20)
C(2)	0.120 5(13)	0.485 8(14)	0.329 2(6)	0.148 8(10)	-0.061 6(24)	0.384 0(20)
Br(2)	-0.107 7(2)	0.459 1(2)	0.304 83(7)	0.144 2(1)	-0.288 7(3)	0.449 6(3)
C(3)	0.219 0(14)	0.584 0(13)	0.295 8(6)	0.096 5(9)	0.035 3(26)	0.400 0(25)
C(4)	0.388 5(14)	0.603 2(14)	0.314 4(6)	0.100 3(11)	0.197 4(26)	0.352 5(26)
Br(4)	0.521 6(2)	0.743 7(2)	0.269 08(7)	0.028 1(1)	0.334 3(3)	0.368 1(4)
C(5)	0.460 7(15)	0.531 0(14)	0.366 4(6)	0.152 2(9)	0.262 7(20)	0.292 5(23)
C(6)	0.356 7(15)	0.431 5(13)	0.400 3(6)	0.203 1(9)	0.163 9(22)	0.278 2(23)

aromatic system. Relative ring dispositions (Figures 2 and 3) show that in both cases, the closest inter-segment contact will be between a C(6) hydroxy-hydrogen and the other phenyl ring; in both compounds, H(6) ··· C(1a) is *ca.* 2.5 Å. The considerable inequivalence in the exocyclic angles at C(1b) in (1) may be considered to arise from this; a similar but less significant discrepancy may be noted in (2). Exocyclic angular discrepancies may also be noted in (1) at C(4). Consideration of Br(4) ··· C(3,5) distances confirms the presence of a molecular distortion here in (1), and (2) in section (a) only; for (1a), the distances are 2.85(1), 2.78(1) Å; for

(1b), 2.83(1), 2.82(1) Å; for (2a), 2.89(2), 2.82(2) Å; for (2b), 2.83(2), 2.84(2) Å.

The phenolic hydrogen in (2) appears to be involved in a contact to Br(2a), Br(2a) ··· O(6a) (*x, y, 1 + z*) being 3.02(1) Å with an associated Br ··· H estimate of 2.7 Å. For (1) the situation is more complex: each phenolic hydrogen appears to be dispersed over a pair of sites, one involving hydrogen bonding to the centrosymmetrically related oxygen atom [O(6a) ··· O(6a) ($\bar{x}, 1 - y, 1 - z$), 2.82(1) Å, with H(6a') ··· O(6a), O(6a) ($\bar{x}, 1 - y, 1 - z$) estimated at 1.2, 2.0 Å (difference map) and O-H-O 126°], while the other involves a contact to the chlorine

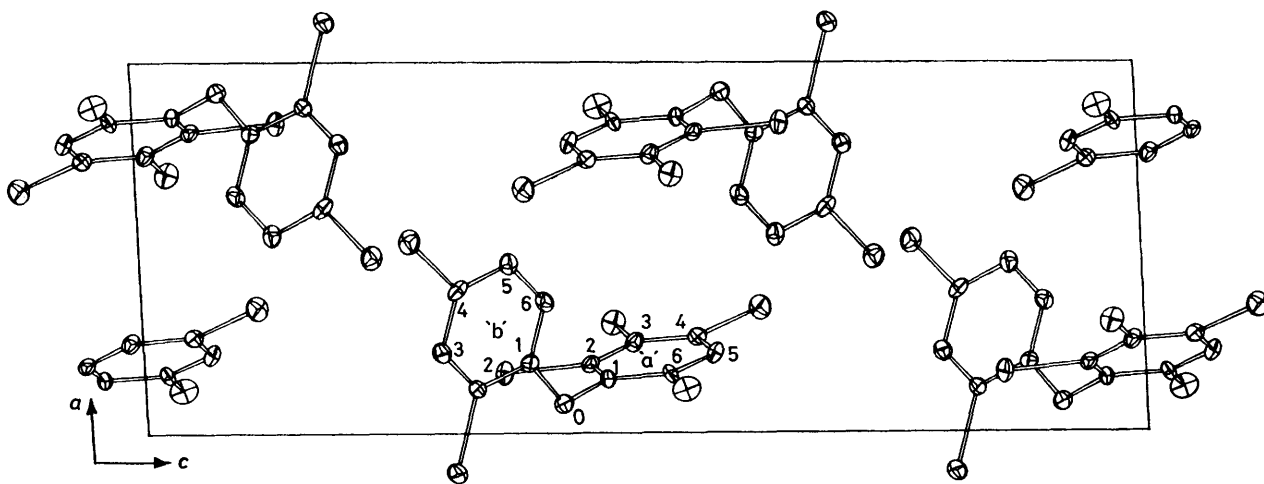


FIGURE 2 Unit cell contents of (1), projected down *b*. Non-hydrogen atoms are shown with 20% thermal ellipsoids. Carbon atom numbering is given

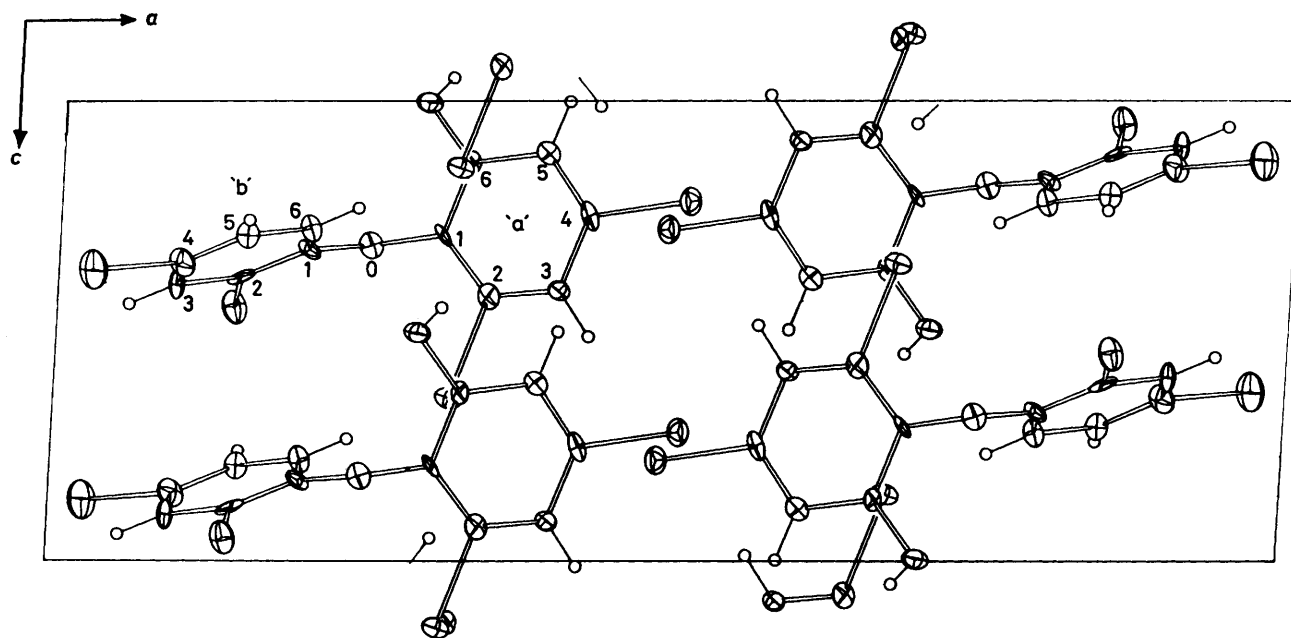


FIGURE 3 Unit cell contents of (2)

TABLE 2

Molecular non-hydrogen atom geometries for (1) and (2)		Parameters			
Atoms		(1)/b	(2)/a	(2)/b	
Compound/section	(1)/a	(1)/b	(2)/a	(2)/b	
Distances/Å					
O(0)-C(1)	1.37(1)	1.37(1)	1.38(2)	1.37(2)	
C(1)-C(2)	1.39(2)	1.38(2)	1.38(3)	1.37(3)	
C(1)-C(6)	1.39(2)	1.35(2)	1.39(3)	1.38(3)	
C(2)-C(3)	1.38(2)	1.37(2)	1.32(3)	1.38(3)	
C(3)-C(4)	1.39(2)	1.38(2)	1.42(3)	1.37(3)	
C(4)-C(5)	1.38(2)	1.37(2)	1.37(3)	1.35(3)	
C(5)-C(6)	1.39(2)	1.41(2)	1.42(3)	1.37(3)	
C(2)-Br(2)	1.87(1)	1.86(1)	1.92(2)	1.91(2)	
C(4)-Br(4)	1.86(1)	1.89(1)	1.91(2)	1.92(2)	
C(3)-Cl(3)	1.72(1)				
C(6)-O(6)	1.34(1)		1.33(2)		
Angles/°					
C(1)-O(0)-C(1)	118.7(8)		118(1)		
O(0)-C(1)-C(2)	119.9(10)	115.7(9)	122(2)	119(2)	
O(0)-C(1)-C(6)	119.0(9)	123.4(10)	119(2)	124(2)	
C(2)-C(1)-C(6)	120.9(10)	120.9(11)	119(2)	117(2)	
C(1)-C(2)-C(3)	120.4(11)	119.6(10)	125(2)	123(2)	
C(2)-C(3)-C(4)	119.1(10)	119.2(11)	117(2)	117(2)	
C(3)-C(4)-C(5)	120.4(11)	122.2(11)	122(2)	123(2)	
C(4)-C(5)-C(6)	121.0(11)	117.5(11)	119(2)	119(2)	
C(5)-C(6)-C(1)	118.2(10)	120.5(11)	119(2)	121(2)	
C(1)-C(2)-Br(2)	118.1(8)	120.6(9)	119(1)	120(2)	
C(3)-C(2)-Br(2)	121.5(9)	119.7(9)	117(1)	117(2)	
C(3)-C(4)-Br(4)	122.0(9)	118.7(9)	120(1)	118(2)	
C(5)-C(4)-Br(4)	117.6(9)	119.0(9)	118(2)	119(1)	
C(2)-C(3)-Cl(3)	120.9(9)				
C(4)-C(3)-Cl(3)	119.9(9)				
C(1)-C(6)-O(6)	119.6(10)		120(2)		
C(5)-C(6)-O(6)	122.2(11)		121(2)		

atom of a molecule in an adjacent cell [Cl(3a) \cdots O(6a) ($x, y - 1, z$), 3.8 Å, Cl(3a) \cdots H(6a) ($x, y - 1, z$), ca.

3.1 Å]. This apparent disorder may be real, or a consequence of the use of a space group of unrealistically high symmetry. We thank one of the referees for bringing this point to our notice.

Note added in proof: The sponge is almost certainly a new genus of the family Callyspongiidae (Order Haplosclerida). We are grateful to Professor Bergquist, University of Auckland, New Zealand, for the classification.

[0/1422 Received, 16th September, 1980]

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