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Crystal structures and isometricity comparison of methylated bisphenol F derivatives

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highlights

_ The X-ray structure of four bisphenol F derivatives are determined.
_ Four methyl groups at bisphenol F do not disturb the strong hydrogen bond network.
_ Methyl groups have a higher structural influence than H donors or acceptors.
_ Isometricity comparison reveals the degree of relationship between the structures.

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abstract

The syntheses and X-ray structures of three methylated bisphenol F derivatives and one respective analogue are reported. A special emphasis lies on the influence of methyl groups on the conformation of the common diphenylmethane scaffold. The introduction of four methyl groups to bisphenol F was found not to disturb its typical strong hydrogen bond network, and yet, to change the pattern of the aromatic interactions in the overall packing. According to the isometricity comparison, the addition of methyl groups to the diphenylmethane core has a greater influence on the conformation of the individual molecules, than the presence or absence of hydrogen bonding donors or acceptors.

1. Introduction

The term ‘bisphenol’ is used for a class of chemical compounds bearing two hydroxyphenyl moieties connected via a carbon or sulfur bridge [1]. For many decades, they are widely used in the manufacturing of epoxy resins and polycarbonates to produce different everyday objects like water bottles, coatings or electronic devices [2]. Though these polymers are more or less uncritical in connection with human health, they are believed to disintegrate liberating harmful bisphenol monomers [3]. One prominent member is bisphenol F featuring a bridging methylene group between the two aromatic units. In this respect, ‘F’ stands for ‘formaldehyde’ from which the actual molecule is synthesized by reaction with phenol. It is believed to interfere with environmental processes and human health, e.g. was found to establish estrogenic activity in in vitro bioassays [4]. Humans can be exposed to bisphenol F and its derivatives as environment and food contaminants [5].

By adding electron donating methyl groups to the aromatic rings of bisphenols they become more lipophilic and sterical demanding. Their respective solubility, bioavailability and biological activity are directly connected to the molecular structure and intermolecular interactions of the particular derivative in the solid state and in solution [6]. Though some compounds of this type were studied according to their medicinal activity [7], the knowledge of methylated bisphenols and their analogues is rather limited

[8]. Here we discuss in detail the crystal structures and solid state behaviour of three bisphenol F derivatives and one respective analogue (1–4). To the best of our knowledge, specifics on the molecular structure of these compounds are missing [9]. In this paper, we present the X-ray structures and deliver an extensive conformational analysis including isometricity comparison. Of special interest in this respect is the influence of different phenyl substituents on the relative position of the aromatic units.

2. Experimental

2.1. Synthesis

Compounds 1–3 (Scheme 1) were prepared analogously to literature protocols, starting with commercially available 2,6-dimethylphenol, which was dimerized by reaction with formaldehyde [10], followed by etherification with methyl iodide [11] and oxidation with CrO_3 [12]. Benzhydrol 4 was obtained from 1-bromo-3,5-dimethylbenzene and ethyl formate via a Grignard reaction [13].

2.2. X-ray structure determination

Crystals of the title compounds suitable for X-ray diffraction were obtained by slow evaporation of respective solutions of 1 in ethyl acetate, 2 in n-hexane, 3 in ethanol and 4 in ethanol, respectively. The X-ray structure of bisphenol F (5) has been published by Lim and Tanski [14] and was included in our discussion for comparison.

The single crystal X-ray diffraction data of compounds 1–4 were collected at 100 K on a Bruker Kappa diffractometer equipped with an APEX II CCD area detector and graphite-monochromatized Mo Ka radiation (k = 0.71073 Å) employing u and x scan modes. The data were corrected for Lorentz and polarization effects. Semiempirical absorption correction was applied using the SADABS program [15]. The SAINT program [15] was used for the integration of the diffraction profiles. The crystal structures were solved by direct methods using SHELXS-97 [16] and refined by full-matrix least-squares refinement against F_2 using SHELXL-97 [16]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were generated at ideal geometrical positions and refined with the appropriate riding model. Geometrical calculations were performed using PLATON [17] and molecular graphics were generated using SHELXTL [16]. The crystallographic data collection and refinement parameters are given in Table 1. Relevant angles and crucial intermolecular contacts are presented in Tables 2 and 3, respectively.

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC 954338 to CCDC 954341). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/datarequest/cif, by e-mailing data-request@ccdc.com.ac.uk or by contacting the Cambridge CB21 EZ, UK; fax: +44 1223 336033.

2.3. Isometricity calculation

The Molecular Isometricity Indeces I(m) [24] for the X-ray structures of 1–4 were calculated by the following equation by leastsquares fitting of the positions occupied by the identical atoms of the two superimposed molecules:

where n is the number of distance differences between the crystal coordinates (DR_i) of identical non-H atoms within the same section of the related structures. The higher the I(m) value, the higher the similarity of the compounds.

While the Isostructurality Index I(s) takes into account both the differences in the geometry of the molecules and the positional differences caused by rotation and translation, the Molecular Isometricity Index I(m) represents solely the differences in the geometry of the molecules neglecting to the placement of the molecule in the asymmetric unit.

3. Results and discussion

3.1. X-ray single crystal analysis

In the structure of tetramethylated bisphenol F 1 the two phenolic moieties are related by a crystallographic twofold rotational

symmetry with the two phenyl rings varying clearly from perpendicularity (67.1_) (Table 2, and Fig. 1). The two angles between the planes of each aromatic unit and the plane defined by C_{aryl}–C_{bridge}–C_{aryl}, the so-called pitch angle, are identical (82.4_) because of the molecular symmetry. In contrast, mother bisphenol 5 [14] displays two different pitch angles (40.7 and 45.7, resp.), as molecular symmetry is not realised in the absence of tetramethylation. Despite the two phenolic groups in 1, the polar solvent, ethanol, used for

crystallization is not incorporated in the crystal as it might have been expected. There is strong intermolecular O–H_ _ _O hydrogen bond with d(O_ _ _O) = 2.857(1) Å between the neighbouring molecules (Table 3). As a result, layers of molecules are formed in the crystallographic ab plane developing p_ _ _p-stacking with the distance of 3.523(2) Å between the parallel but shifted aromatic units (Fig. 2). The layers are supported by a C–H_ _ _O hydrogen bond with d(H_ _ _O) = 2.56 Å. In contrast, the mother compound bisphenol F, which lacks the four methyl groups at the aromatic rings, develops similar strong hydrogen bonds [d(O_ _ _O) = 2.760–2.727 Å] in three dimensions. The edge to face C–H_ _ _p interaction becomes determinant with the distance of 3.598(2) Å due to the enlarged shift of face to face placement of the phenyl rings.

The molecular structure of bismethoxy derivative 2, crystallizing with one and a half molecule in the asymmetric unit, is depicted in Fig. 3. The pitch angles are 60.3_ and 60.5_ for molecule a, which has lower symmetry, and 51.4_ for molecule b, which has higher symmetry, as the molecule is arranged around a twofold axis. Due to the fact that compound 2 lacks of respective donors, no strong hydrogen bonds are to be found in the structure. The packing behaviour influences the molecular conformation rather interestingly. Molecule a constructs a layer in the crystallographic bc plane solely developing van-der-Waals interactions among the molecules. Molecule b is engaged in C–H_ _ _p-interactions involving its methoxy group and its aromatic ring, which result in a handshake-like motif, connecting the molecules in a chain along the crystallographic c axis. As a result, molecule b has lower degree of freedom, therefore it develops a higher symmetry. The overall

packing of the two different motifs is only realized by C–H_ _ _Ocontacts (Fig. 4, and Table 3).

As expected, the oxidation of the bridging methylene group of tetramethylbisphenol F into a carbonyl function in compound 3 (Fig. 5) is accompanied with an enlarged C_{aryl}–C_{bridge}–C_{aryl} angle (118.4_). The introduction of four methyl groups to the aromatic rings of dimethoxybenzophenone decreases this angle, compared to the two polymorphs of the unmethylated molecule (monoclinic

[18]: 120.6/120.3_; triclinic [19]: 120.0/119.5_). The rigid carbonyl group of 3 also gives rise to lower dihedral and pitch angles of 54.9_ and 33.0/31.1_, respectively, which is a common feature of benzophenones [20]. Due to the rather nonpolar character of the molecule and the isolated keto function the intermolecular interactions of the molecules in the packing is restricted to weak C–H_ _ _O hydrogen bonds with d(H_ _ _O) = 2.45–2.54 Å between the methoxy oxygens and three methyl groups forming a chain of molecules in the direction of c crystallographic axis as shown in Fig. 6.

Crystallization of benzhydrol derivative 4 from ethanol gives monoclinic crystals in the space group $P2_1/n$, in which the polar protic solvent is not included (Fig. 7). By way of interest, the two aromatic moieties exhibit rather different pitch angles (81.1_ and 33.5_), which is an uncommon feature for the here presented class of compounds. The hydroxyl group of 4 is engaged in strong intermolecular O–H_ _ _O hydrogen bonds (Table 3) forming columns of the molecules in direction of the crystallographic b axis. Noteworthy, the d(O_ _ _O) = 2.751(2) distance is rather short in comparison to the crystal structure of the benzhydrol mother compound [d(O_ _ _O) = 2.878 and 2.826 Å] [21]. This shorter hydrogen bond in 4 is accompanied by C–H_ _ _p-interactions involving the methin

proton. An analogous feature has also been observed in the structures of hydroxymethyl derivatives of polynuclear aromatic hydrocarbons such as anthracene [22] or pyrene [23]. (see Fig. 8)

3.2. Comparison of the X-ray structures

In order to quantify the similarity of two or more molecules, the Molecular Isometricity Index I(m) has proven as a useful instrument [24]. It is a direct measure for the degree of approximate isomorphism of the species compared, and therefore markedly well suited to examine to conformational influence of different substituents on a common core structure (Scheme 2). In our case, we consider the diphenylmethane moiety as such, and discuss in the following the influence of hydroxyl, methoxy and methyl groups on its conformation in the respective crystal structures of 1–5 (Tables 4 and 5).

Although both crystals of 1 and 2 are found in space group C2/c, the content of the asymmetric unit differs: there is 0.5 molecule in 1 and 1.5 molecules in 2. The symmetric molecules in both crystals are organized by a twofold axis. 1 and 2 only differ in the para-phenyl substituent, as the hydroxyl groups are replaced by methoxy groups. This derivatization increases the size of the molecule and together with a lower molecular symmetry result in a tripled unit cell volume (4869.4(5) Å$_3$ for 2 vs. 1344.8(2) Å$_3$ for 1). The Molecular Isometricity Indices for the comparison of 1:2a (88.1%) and 1:2b (83.1%) (Scheme 2a) prove medium geometrical similarity of the two frameworks. Dealing with the structure of 2, we compared the two crystallographically independent molecules: The calculated I(m) value of the two chemically identical but crystallographycally different molecules is only moderate (82.2%). As shown in Fig. 9, this rather low similarity [25] is caused to a large extent by the methoxy groups on both ends of the molecules, which are on the opposite side of the phenyl rings.

The only chemical difference between molecules 2 and 3 is the keto oxygen substituent on the central carbon atom. This is responsible for a considerable lower dihedral angle in ketone 3 than in bisphenol derivative 2 and moderate Molecular Isometricity Indices of 85.0% for 2a:3 and 81.3% for 2b:3 (Scheme 2b).

Fig. 8. Depiction of the hydrogen bonding network of benzhydrol 4 along the crystallographic b axis. Dashed lines represent hydrogen bonds.

Scheme 2. Compared moieties from different structures discussed in this paper.

Fig. 9. The two crystallographically independent molecules in structure 2. The largest difference is the relative position of the methoxy groups, caused by the different intermolecular interactions of the two molecules.

Compounds 1–4 contain the common bis(3,5-methylphenyl) methane moiety (Scheme 2c) with the influence of the different substituents on this more distinct framework characterized in Table 4. In general, the different placement of the hydroxyl group in 1–4 changes the arrangement of the molecules in the crystals. The space groups are different, the molecular geometries are moderately similar. Hence, the two crystallographically independent molecules a and b in the structure of 2 show the highest similarity of all examined pairs (94.0%). The lowest correlation is observed for the pair 1:3 (70.4%), which can be explained with the severe chemical difference of the two compounds. Interestingly, the conformation of bis(3,5-methylphenyl)methane with two methoxy groups in para-position (2) is closer related to the respective benzhydrol 4 (90.1% and 89.7%) than it is to its parent compound 1 (86.8% and 81.2%).

Comparing the 13 carbon atoms of the diphenylmethane core (Scheme 2d) in all five crystal structures revealed varying molecular similarities (Table 5, and Fig. 10). The most similar pairs are 2b:5 (95.7%) and 2a:2b (95.6%), indicating a close conformational relationship. Most striking is the high I(m) value (94.7%) for keton 3 and bisphenol F (5) as they are chemically rather different. Interestingly, chemically more closely related pairs as 1:5 show only slight similarity (82.5%), even though both develop analogous hydrogen bonding. The pitch angle of 1 (82.4_) is considerably larger than the one in bisphenol F (40.7_ and 45.7_), which causes the rather low I(m) value and is a direct result of the methyl groups attached to the bisphenol.

4. Conclusions

The crystal structures of three bisphenol F derivatives and one respective analogue featuring each four methyl groups at the diphenylmethane moiety have been determined. In order to elucidate the structural relationship of this compound family isometricity calculations were performed. These provide the information as given in the following.
(1) All bisphenols presented here show no inclusion properties, though the diphenylmethane building block is a known scaffold in supramolecular chemistry. (2) Introduction of four methyl groups to bisphenol F does not disturb its typical strong hydrogen bond network, and yet, changes the pattern of the aromatic interactions in the overall packing. (3) Methylation of the characteristic phenol groups reduces the intermolecular interactions to weak C–H_ _ _O and C–H_ _ _p-contacts. (4) Strong hydrogen bonds in the overall packing cause lower conformational flexibility of the respective molecules. (5) According to the isometricity comparison, the addition of methyl groups to the diphenylmethane core has a greater influence on the conformation of the individual molecules, than the presence or absence of hydrogen bonding donors or acceptors.

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